The Kinetics and Mechanisms of Additions to Olefinic Substances. Part 13.[1] Reactions of 3-Substituted Cholest-5-enes with Sources of Electrophilic Bromine

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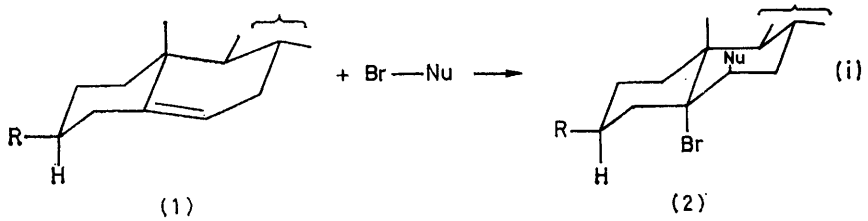
The kinetics of second-order bromination in acetic acid, and of third-order bromination in chlorobenzene, have been examined for a series of 3β-substituted cholest-5-enes; the results confirm that the rates of these reactions are subject to polar influences approximately of the magnitude expected for a substituent insulated by two saturated carbon atoms from the site of development of the carbocationic centre. The products of reactions of a number of these substrates with sources of electrophilic bromine and chlorine, in chlorobenzene, chloroform, and acetic acid as solvents, have been investigated by ^{1}H n.m.r. spectroscopy. In most cases the main products are the expected 5α-halogeno-6β-substituted adducts. 5β,6α-Adducts are formed in minor amounts also in the bromination of 3β-trifluoroacetoxycholest-5-ene, and in the reactions of a number of 3β-substituted cholest-5-enes with bromine chloride in deuteriochloroform and in chlorobenzene. Some of the mechanistic implications of these findings are discussed.

THE rates of bromination of a number of 3β-substituted cholest-5-enes and of 3β,17β-disubstituted androst-5-enes have been measured by Schwarz and his co-workers.[2] The influence of structure on the rate of reaction has been interpreted as implying that in the rate-determining ring A. Analogous additions in which non-Markownikoff orientation is determined by steric hindrance to the completion of the reaction have been described.[10]

The account of these brominations given above provides a satisfactory description of the reaction pathways,



(1) (2)

transition state carbocationic character is more prominently developed on the 5- than on the 6-carbon atom,[2,3] as would be expected on electronic grounds and in view of the orientation of addition of hydrogen chloride to cholest-5-ene.[4,5] With unsymmetrical reagents supplying electrophilic bromine, however, completion of the reaction gives the 5-bromo-product [6-9] [reaction (i)]. When such reactions are two-stage processes, therefore, the transition states for the two stages are probably best represented as (3) and (5). In (3), axial approach by halogen allows weak bridging between the 6- and 5-positions to become established, giving an unsymmetrical bridged bromo-substituted carbocation (4). Attack by the nucleophile as in (5) occurs more readily at the 6-position, displacing bromine and allowing it to move smoothly to its 5α-location; the alternative attack by the nucleophile at the 5β-position is impeded by steric congestion and by resistance to conformational change in but it leads to the formulation of a number of further questions which are so far unanswered. For example, the kinetic form, and hence the transition state, relevant to the formation of the known products of bromination is not certain. Schwarz and his co-workers [2] describe their brominations as being of the second kinetic order ($-d[Br_2]/dt = k_2[S][Br_2]$) in acetic acid–chloroform at *ca.* 0.007M. In the light of earlier work,[11,12] it seems unlikely that this kinetic form is actually adopted; reactions of order greater than one in bromine are commonly encountered in solvents of this kind. A further kinetic possibility which has not been discussed invokes an Ad_E3 pathway,[13-15] with a transition state such as (6); in such a pathway, the polar effects of remote substituents might well be modified. The factors which determine the extent to which products of 6β-electrophilic attack on the cholest-5-ene system will be formed are also worthy of more detailed analysis.

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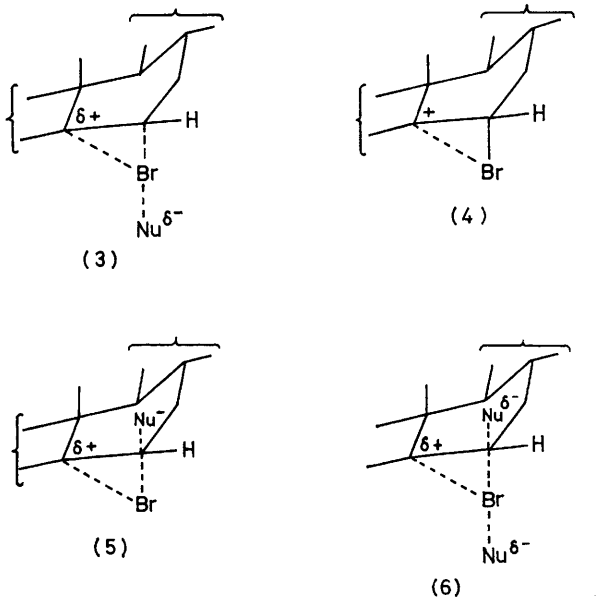
We now present some new experimental information which helps to clarify some of these matters, complementing results presented in an accompanying paper



comparing reactions of 3β-substituted cholest-5-enes with those of cholest-5-en-3-one.

EXPERIMENTAL

Some of the materials and methods have been described in earlier papers.[1,16-18] The methods used to prepare and characterise other known compounds are given in Supplementary Publication No. SUP 22098 (43 pp.),* where ^{1}H n.m.r. spectra of these compounds and of others described in this paper are given also. Tetraphenylarsonium chloride (Fluka, laboratory reagent grade) was dried *in vacuo* (P_2O_5) and stored in a desiccator.

6β-Acetoxy-5α-bromocholestan-3β-ol was prepared by treating cholesterol (10 g) with bromine acetate [8] (1 mol. equiv.) in CCl_4 (300 cm^3) at 0 °C for 10 min. The solution was then washed successively with aq. Na_2SO_3 and water, and dried ($MgSO_4$). Removal of solvent gave a slightly impure product which formed a gel on attempted crystallisation from a number of solvents. The gel from n-hexane after being dried *in vacuo* had m.p. 156—157° (Found: Br, 15.9. $C_{29}H_{49}BrO_3$ requires Br, 15.2%). Acetylation gave 3β,6β-diacetoxy-5α-bromocholestane, m.p. 93—96° (from methanol) (lit.,[8] 89—91°), not depressed on admixture with an authentic sample, m.p. 94—96°, prepared as described in the literature; [8] the ^{1}H n.m.r. spectra of the two specimens were identical.

3β-Trifluoroacetoxycholest-5-ene was prepared by treating cholesterol (7.5 g) with trifluoroacetic anhydride (25 cm^3) at room temperature for 18 h. The mixture was then poured into ether (500 cm^3) and washed repeatedly with aq. $NaHCO_3$ and with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The solid residue was crystallised from ethyl acetate–methanol and gave needles (6 g), m.p. 132.5—133 °C, δ ($CDCl_3$) 0.69 (3 H, s, 18-H_3), 1.05 (3 H, s, 19-H_3), 2.44 (d, J 8 Hz, 4-H_2), 4.77vbr (1 H, m, 3α-H), and 5.41 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 6-H) (Found: C, 72.3; H, 9.1; F, 11.6. $C_{29}H_{45}F_3O_2$ requires C, 72.2; H, 9.4; F, 11.8%).

4,4-Dideuterio-3β-trifluoroacetoxycholest-5-ene was prepared similarly from 4,4-dideuteriocholestrol; [17] m.p. 131—131.5 °C, δ ($CDCl_3$) 0.70 (3 H, s, 18-H_3), 1.06 (3 H, s, 19-H_3), 4.78 (1 H, 2d, $J_{2\alpha,3\alpha}$ 5, $J_{2\beta,3\alpha}$ 10 Hz, 3α-H), and 5.42 (1 H dd, $J_{6,7\alpha}$ 1.7, $J_{6,7\beta}$ 4.8 Hz, 6-H); the ^{1}H n.m.r. spectrum showed that it contained more than 90% of deuterium at the 4α- and 4β-positions.

Chlorobenzene (M & B, laboratory reagent grade) was shaken with acidified iron(II) sulphate solution to remove peroxides, washed (H_2O, $NaHCO_3$, and H_2O), dried ($CaCl_2$), and fractionally distilled; the fraction collected had b.p. 132° at 753 mmHg, and was stored over molecular sieves in the dark.

Deuteriochloroform (B.D.H., laboratory reagent grade) was shaken with acidified iron(II) sulphate solution, washed (H_2O, $NaHCO_3$, and H_2O), dried ($CaCl_2$) under nitrogen, and fractionally distilled under nitrogen; the fraction collected had b.p. 58.5—59.0° at 750 mmHg, and was used immediately.

Products of reactions in deuteriochloroform were examined by ^{1}H n.m.r. spectroscopy without work-up. Products of reactions in chlorobenzene were worked up by careful removal of the solvent under high vacuum at 30—40 °C, and the residual oils were dissolved in $CDCl_3$ and examined by ^{1}H n.m.r. spectroscopy. Reaction mixtures in acetic acid were poured into an excess of aqueous potassium iodide and sodium thiosulphate and then the products were extracted with diethyl ether. The extract was then washed first with water, then with aq. $NaHCO_3$ (5%) until neutral to litmus, and then dried ($MgSO_4$). The solvent was then removed carefully under reduced pressure at 30—40 °C, and the residual oil was dissolved in $CDCl_3$ and examined by ^{1}H n.m.r. spectroscopy.

Solutions of bromine chloride were prepared by mixing equimolar amounts of bromine and chlorine in the required solvent.

Products of Reactions with Bromine in Deuteriochloroform.—To cholesterol (2×10^{-4} mol) was added bromine (2.5×10^{-4} mol) in $CDCl_3$ (0.5 cm^3) at *ca.* 20 °C. When the reaction was visibly complete, the mixture was examined by ^{1}H n.m.r. spectroscopy. The sole detected product was 5α,6β-dibromocholestan-3β-ol, which was spectroscopically identical with an authentic sample. The mixture was then stored at 37 °C for several days, its spectrum being scanned at intervals; the 5α,6β-dibromide was converted slowly into an equilibrium mixture containing *ca.* 20% of 5α,6β- and *ca.* 80% of 5β,6α-dibromocholestan-3β-ol, recognised by its spectrum (identical with that of an authentic sample).

Similar results were obtained for 3α-benzoyloxycholest-5-ene and for a series of 3β-substituted cholest-5-enes (3β-H, MeO, AcO, $PhCO_2$, or $F_3C{\cdot}CO_2$), the spectra of the isomeric dibromides being almost indistinguishable from those of the cholesterol dibromides except for differences in the 3-H signal. 3β-Chlorocholest-5-ene also gave the 5α,6β-dibromide; no rearrangement to the 5β,6α-isomer was observed, presumably because the equilibrium is unfavourable

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin II*, 1976, Index issue.

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

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

as result of the 3β,5β-diaxial interaction between chlorine and bromine in the 5β,6α-dibromide.

5α,6β-Dibromides were produced also from cholest-5-en-3α-ol and from 3α-methoxycholest-5-ene. Both these substrates gave also much unidentified material, the spectrum of which included multiplets in the region δ 3—7.

Products of Reactions with Bromine in Chlorobenzene.—Treatment of 3β-benzoyloxycholest-5-ene (0.005M) at 25 °C in the dark with bromine (0.005M) in PhCl with added 1M-2-methyloxiran gave the 5α,6β-dibromide as the only detected product.

Products of Reactions with Bromine in Acetic Acid.—3β-Acetoxycholest-5-ene (0.02M) was treated with bromine (0.02M) in acetic acid containing NaOAc (0.02M) for 5 min at 25 °C in the dark. Work-up gave the 5α,6β-dibromide (90%) and the 5α-bromo-6β-acetoxy-adduct (10%), recognized by its ^{1}H n.m.r. spectrum (identical with that of an authentic specimen). Similarly 3β-trifluoroacetoxycholest-5-ene (0.005M) and bromine (0.005M) in acetic acid containing NaOAc (0.02M) for 200 min at 25 °C in the dark gave the 5α,6β-dibromide (*ca.* 80%), the 5β,6α-dibromide (5%), and the 6β-acetoxy-5α-bromo-adduct (*ca.* 15%).

Products of Reactions with Bromine Chloride.—(a) *In acetic acid.* 3β-Trifluoroacetoxycholest-5-ene (0.005M) was treated with BrCl (0.005M) in HOAc containing NaOAc (0.02M) at 25 °C for 3 h. Work-up gave a mixture containing, as far as could be detected by ^{1}H n.m.r. spectroscopy, only the 5α-bromo-6β-chloro-adduct (*ca.* 65%) and the 5α-bromo-6β-acetoxy-adduct (*ca.* 35%).

(b) *In deuteriochloroform and in chlorobenzene.* To each of a series of 3-substituted cholest-5-enes (3-H,β-HO, β-MeO, β-$MeCO_2$, β-Cl, β-$CF_3{\cdot}CO_2$, β-$PhCO_2$, or α-$PhCO_2$) (2×10^{-4} mol) was added bromine chloride (2.5×10^{-4} mol) in deuteriochloroform (0.5 cm^3) at room temperature; when the reactions were visibly complete (less than 5 min), the solutions were examined by ^{1}H n.m.r. spectroscopy. Each product mixture contained *ca.* 10% each of the 5α,6β-dibromo- and 5α,6β-dichloro-adducts, recognised from their spectra.

The major component of the remaining products from cholesterol had a spectrum identical with that of authentic 5α-bromo-6β-chlorocholestan-3β-ol; the major component in each of the other product mixtures had precisely the same spectral characteristics and was clearly the 5α-bromo-6β-chloro adduct.

Each of the reaction mixtures contained another minor component, detectable only by the presence of a multiplet ($W_{\frac{1}{2}}$ 6—8 Hz) *ca.* 0.1 p.p.m. upfield from and partially overlapped by the multiplet ($W_{\frac{1}{2}}$ *ca.* 7 Hz) corresponding to 6α-H of the 5α-bromo-6β-chloro-adduct. The corresponding 6α-H signals in the spectra of 5α-chloro-6β-bromo- and 5α-bromo-6β-chloro-cholestan-3-one (accompanying paper) are in the same relative positions; by analogy, this minor component is probably the 5α-chloro-6β-bromo-adduct.

A further minor component, present in each of the product mixtures except that from 3β-chlorocholest-5-ene, could only be detected by the presence of a small singlet at δ 0.65—0.69 (*ca.* 0.05 p.p.m. upfield from the 18-H_3 signals for the 5α,6β-dihalogeno-adducts, which are in the range δ 0.69—0.73). The corresponding 5β,6α-dichlorides and dibromides have 18-H_3 signals in this region, and the relative proportions of this component in the above product mixtures decreased with increasing electronegativity of the 3-substituent in the same manner as does the proportion of 5β,6α-dichloride in the products from chlorination of the same compounds (see below). This minor component is therefore probably one or more 5β,6α-dihalogeno-adducts.

TABLE 1

Product proportions from the reactions of 3-substituted cholest-5-enes (0.4M) with bromine chloride (0.5M) in deuteriochloroform at 18—20 °C in the dark

		Product proportions (%)			
3-Substituent	Added substance	5α-Br,6β-Cl adduct	5α-Cl,6β-Br adduct	5β,6α-Adducts	5α,6β-Dibromide and dichloride *
H		62	3	15	20
β-HO		65	3	12	20
β-MeO		65	3	12	20
β-$MeCO_2$		67	3	10	20
β-$PhCO_2$		72	3	8	20
β-$PhCO_2$	Ph_4AsCl (0.4M)	97	3		
β-Cl		77	3		20
β-$CF_3{\cdot}CO_2$		74	3	3	20
α-$PhCO_2$		73	3	4	20

*Approximately equal amounts.

The product proportions from the above reactions, and the results of similar bromochlorinations in $CDCl_3$ with various added substances, are given in Table 1. Similar results obtained in chlorobenzene as solvent are given in Table 2.

Products of Reaction with Bromine Acetate.—To each of a selection of 3-substituted cholest-5-enes (3-H, β-HO, β-$MeCO_2$, β-$CF_3{\cdot}CO_2$, or α-$PhCO_2$) (2×10^{-4} mol) was added bromine acetate (4×10^{-4} mol) in chlorobenzene (4 cm^3) at 0 °C. The mixtures were kept at 0 °C in the dark for 2 h, then worked up, and the products were examined by ^{1}H n.m.r. spectroscopy. The sole detected products from cholesterol and cholesteryl acetate were their 5α-bromo-6β-acetoxy-adducts, identical (spectra) with authentic samples. The other substrates (3-H, β-$CF_3{\cdot}CO_2$, or α-$PhCO_2$) also gave only one detected product whose spectrum was clearly that of a 5α-bromo-6β-acetoxycholestane.

Similar bromoacetoxylation of cholest-5-ene in the presence of 2-methyloxiran (2M) gave 6β-acetoxy-5α-bromocholestane as the sole detected product.

Kinetics of Bromination.—Since comparison was ultimately intended between reactions of 3-substituted cholestanes and those of cholest-5-en-3-one, a suitable base was included in our reaction mixtures in order to neutralise HBr or HCl developed during the reaction and potentially

capable of catalysing subsidiary changes. Light was excluded from all reacting mixtures.

In acetic acid. Rates of bromination in acetic acid containing sodium acetate (0.02M) were determined conventionally; [11] full details of the procedure are given in the Supplementary Publication. Second-order rate-coefficients for results obtained at concentrations of bromine in the range 0.0008—0.0002M were constant within experimental error over at least 50% reaction. Values are summarised in Table 3.

At higher concentrations of bromine, the reaction order in bromine was greater than unity, a result consistent with findings of earlier workers.[11] For example, with $[Br_2]$ initially 0.0055M, the initial second-order rate coefficient for 3β-trifluoroacetoxycholest-5-ene was 1.3 l mol^{-1} s^{-1}, and fell as the reaction proceeded in the manner expected for a reaction of mixed kinetic form.

TABLE 2

Product proportions from the reactions of 3-substituted cholest-5-enes (0.025M) with bromine chloride (0.028M) in chlorobenzene * at 0 °C in the dark

		Product proportions (%)			
3-Substituent	Added substance	5α-Br,6β-Cl adduct	5α-Cl,6β-Br adduct	5β,6α-Adducts	5α,6β-Dibromide and dichloride †
H		58	3	15	25
β-$MeCO_2$		62	3	10	25
β-$PhCO_2$		64	3	8	25
β-$CF_3{\cdot}CO_2$		69	3	3	25
β-$CF_3{\cdot}CO_2$	2-Methyloxiran (1M)	69	3	3	25

* Reaction time 2 h. † Approximately equal amounts.

TABLE 3

Second-order rate-coefficients (k_2) for bromination of 3β-substituted cholest-5-enes in acetic acid containing sodium acetate (0.02M) at 25 °C with reactants initially 0.0005M

3β-Subst.:	HO	MeO	AcO	Cl	$CF_3{\cdot}CO_2$ *
k_2/l mol^{-1} s^{-1}:	10.4 ±0.3	8.33 ±0.25	1.67 ±0.06	0.864 ±0.06	0.241 ±0.008

* 4,4-D_2, 0.260 ± 0.008.

In chlorobenzene. The conventional method of quenching reaction mixtures after partial reaction for estimation of the halogen concentration by iodometry has dangers for reactions carried out in aprotic solvents; [12] two phases are produced, and the results can become inaccurate to a major, non-reproducible, extent. For this reason, we used a modification of de la Mare, Scott, and Robertson's [12] method. Into a small, dark brown, nitrogen-filled glass bottle equipped with a stirrer was weighed an appropriate amount of olefin (*ca.* 10^{-4} mol) and, after the addition of solvent (10 cm^3 of PhCl containing 2-methyloxiran), the vessel was tightly stoppered and placed in a water bath maintained at 25.0 (±0.01) °C in a dark-room illuminated by a dim red light. After *ca.* 30 min, the bottle was removed from the bath and the equivalent amount of bromine (*ca.* 10^{-4} mol) in the same solvent (10 cm^3) was added with rapid stirring, and then the vessel was returned to the thermostat.

At appropriate intervals, aliquot parts (2 cm^3) were withdrawn and added, with vigorous swirling, to an excess (25 cm^3) of standardised sodium arsenite (0.001M in 5% $NaHCO_3$). The unchanged arsenite was then back-titrated with standard iodine (0.001M), sodium starch glycolate being used as indicator.

The bromination of each of the olefins investigated followed the general equation $-d[Br_2]/dt = k_3\,[olefin][Br_2]^2$ over at least 75% reaction. Plots of $[Br_2]^{-2}$ against elapsed time ($[olefin]_0 = [Br_2]_0$) were linear with correlation coefficients all in the range 0.998—1.000. The orders in olefin (1) and bromine (2) were confirmed by carrying out runs with equal and unequal initial concentrations of bromine and 3β-chlorocholest-5-ene. Results are given in the Supplementary Publication. Third-order rate-coefficients (k_3) and their standard deviations for several cholestenes ($[olefin]_0 = [Br_2]_0 = ca.$ 0.005M) were computed using a least squares program and are reported in Table 4. Values for cholesterol and cholesteryl acetate, though less satisfactory than for the other compounds because the reactions were so rapid, are included in order to provide as extensive as possible a comparison with results obtained in acetic acid. Unfortunately cholesteryl benzoate is too insoluble for examination in the latter solvent.

On reviewing the rapidity of the brominations in acetic acid and in chlorobenzene investigated in this work, we felt that the rate coefficients reported by Schwarz and his coworkers [2] for the bromination of 3β-substituted cholest-5-enes in chloroform–acetic acid were surprisingly small. Consequently we have re-investigated briefly the bromination of 3β-acetoxycholest-5-ene, under conditions closely similar to theirs. Neither of the methods already mentioned is satisfactory for this solvent mixture; direct quenching of the reaction mixture gives incorrect results for the reasons already given; [12] and acetic acid interferes with the arsenite method. Instead, we used a variant in which the sample removed for titration was added to a vigorously stirred solution of potassium iodide containing a known excess of standardised sodium thiosulphate; the mixture was then back-titrated with standard iodine. This method depends for its success on the fact that iodine is never liberated in the quenching solution, and hence cannot be back-extracted into the precipitated chloroform containing the unchanged reactant. Results of an illustrative kinetic run are given below. The reaction mixture initially contained 3β-acetoxycholest-5-ene (0.00180M) and bromine (0.00141M) in acetic acid (1 part by volume) and chloroform (2 parts by volume) at 25 °C. Aliquot parts (2 cm^3) were removed at intervals and added to a mixture containing an excess of $Na_2S_2O_3$. Back-titration with 0.001874M-I_2 in KI gave the results in Table 5, the zero value being obtained from a control determination in which no steroid was present. The

formal second-order rate-coefficient calculated from these results is for $x = 50\%$, $k_2 = 0.93$ l mol^{-1} s^{-1}.

A kinetic run using 3β-acetoxycholest-5-ene (0.003266M) and bromine (0.002951M) gave $k_2 = 2.44$ l mol^{-1} s^{-1}. Comparison of these results shows that the reaction is of order greater than one in bromine, despite the fact that second-order rate-coefficients are approximately constant within a single kinetic run. The reactions in the chloroform–acetic acid are of rate similar to those in chlorobenzene, and much faster (*ca.* 10^3 times) than those recorded by Schwarz *et al.*[2] Since the latter authors give no experimental details, speculation on the reason for the difference is not profitable.

TABLE 4

Third-order rate-coefficients (k_3) for bromination of 3β-substituted cholest-5-enes in chlorobenzene containing 2-methyloxiran (0.1M) at 25 °C with reactants initially 0.005M

3β-Subst.:	β-OH	β-$MeCO_2$	α-$PhCO_2$	β-$PhCO_2$	β-Cl	β-$CF_3{\cdot}CO_2$
k_3/l^2 mol^{-2} s^{-1}:	9 000 ± 1 000	700 ± 200	281 ± 3	185 ± 4	70 ± 2*	7.8 ± 0.1 †

* With 2-methyloxiran (1.0M) 140. † 4,4-D_2, 8.0 ± 0.2

TABLE 5

Time (s):	0	45	250	480	900	1 500	2 400	7 800
Titre (cm^3 0.001 874M-I_2):	3.80	3.95	4.30	4.50	4.75	4.95	5.15	5.30
Bromine consumed (x, %):	0	10.0	33.3	46.7	63.3	76.7	90.0	100.0

DISCUSSION

Kinetics of Bromination; Structural and Solvent Effects on the Reaction Rates.—The kinetics of the brominations examined in the course of this work accord with those found earlier.[11,12] For rate comparisons, reactions in acetic acid containing sodium acetate were studied at dilutions sufficient to establish the dominance of the second-order form ($-d[Br_2]/dt = k_2[\text{olefin}][Br_2]$); at the higher concentrations needed for product analyses, the third-order form ($-d[Br_2]/dt = k_3[\text{olefin}][Br_2]^2$) was shown to contribute to the rate equation. At concentrations sufficient to make this term dominant, the reactions were too fast for measurement by conventional methods. The latter kinetic form was, however, dominant in solvent chlorobenzene, to which we added 0.1M-2-methyloxiran to ensure that any hydrogen bromide produced by substitution was removed as it was formed. Increasing the concentration of 2-methyloxiran to 1.0M did not affect the products of reaction (see also accompanying paper) but increased the rate (Table 4), no doubt through the expected [19] environmental effect of increased polarity of the solvent on a transition state more polar than the initial state. 4-H/D-Isotope effects are small, as expected.

As found before,[12] third-order brominations remain dominant to lower concentrations in chlorobenzene than in acetic acid; and are less rapid, the former solvent having less effective polarity than the latter. The present results confirm also the observation,[12] previously based on only one rate comparison, that third-order brominations in chlorobenzene are spread by substituent effects more powerfully than are the corresponding reactions in acetic acid.

Other workers,[2,3] in attempts to put such a comparison on a quantitative basis through the use of a linear free-energy relationship, have used Taft, Deno, and Skell's [20] σ_I values as standards of comparison. In Table 6, we give the values of σ_I which we have adopted for the present comparison, together with relative rates of third-order brominations of some allyl derivatives reported by Robertson and his co-workers and summarised in ref. 13.

A value of σ_I (0.67) for the trifluoroacetoxy-group has been estimated from measurements of nuclear quadrupole moments; [21] although this is qualitatively as would be expected, results for other substituents estimated similarly do not give confidence in the numerical accuracy of values determined by using this correlation. We have, therefore, neglected this substituent in estimating a value of ρ_I (*viz.* −5.1) from the results given in Table 3. This represents a quantitative, albeit approximate, measure of the effect of a substituent R on the rate of bromination of R·$\dot{C}$H·CH_2·$\dot{C}$:CH− in a 3β-substituted steroid. The corresponding effect of R on the rate of bromination of $RCH_2{\cdot}CH{:}CH_2$ as derived from Table 6 is represented by a ρ_I value of −8.2.

TABLE 6

Values of σ_I, and of relative rates of third-order bromination of $RCH_2{\cdot}CH{:}CH_2$ in acetic acid at 25 °C

R:	HO	EtO	$PhCO_2$	AcO	Cl
σ_I: [a]	0.25	0.25 [b]	0.36 [c]	0.39	0.47
Rel. rate of third-order bromination (HOAc M/80, 25 °C)		51.9	8.8	6.3	1.0

[a] Values from ref. 20 except where otherwise noted. [b] Assumed equal to σ_I for R = MeO. [c] Estimated by interpolation from the graph of $\log_{10}$ (rel. rate) against σ_I. A related estimate, $\sigma_I = 0.40$, can be derived from the relative rates of third-order iodinations given by N. J. Bythell and P. W. Robertson (*J. Chem. Soc.*, 1938, 179).

Interpretation of the difference between these values is possible, because it has been shown [15] that third-order brominations in acetic acid respond to substituents only slightly less powerfully than do the corresponding second-order brominations (for ring-substituted styrenes, ρ for k_2 is −4.8 and for k_3 −4.6). The ρ_I value of −8.2 for third-order bromination of the system $RCH_2{\cdot}CH{:}CH_2$ should be reduced in the steroid system by a factor which has been calculated [3] as being *ca.* 0.6; *i.e.* to ρ_I of *ca.* 5;

[19] E. D. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 763.
[20] R. W. Taft, N. C. Deno, and P. S. Skell, *Ann. Rev. Phys. Chem.*, 1958, **9**, 287.
[21] D. Biedenkapp and A. Weiss, *J. Chem. Phys.*, 1968, **49**, 3933.

and (as observed) second-order bromination should have a similar, perhaps slightly larger value. The good quantative agreement is probably fortuitous, but the results accord well with the view [2,3] that, in the transition state for the rate-determining stage of these brominations, considerable carbocationic character has developed on C-5.

A value of ρ_I (*viz* −7.1) can be derived for third-order brominations in chlorobenzene by plotting the results in Table 4 against those in Table 3. This allows inclusion of the results for the trifluoroacetoxy-substituted compounds, for which the most accurate rate measurements are available. The difference between the results for these brominations accords qualitatively with the earlier finding [12] that structural changes produces rate changes larger for brominations in chlorobenzene than for the corresponding reactions in acetic acid. Such a result is consistent with the view that substituent effects are expected to be larger for a reaction which is slower because it obtains less help from solvation.

In passing, we note that, to the approximation that σ_I and $\log_{10} k^{rel}$ for bromination are connected through a linear free-energy relationship, the value of σ_I for the trifluoroacetoxy-group can be estimated from the rate of second-order bromination of 3β-trifluoroacetoxycholest-5-ene as +0.57; see also Table 6 for values of σ_I for the benzoyloxy-group derived from results of third-order bromination and iodination.

Despite what we believe to be the unsatisfactory nature of the rate measurements of Schwarz *et al.*,[2] the value of ρ_I (−6.3) derived from their rates of bromination in chloroform–acetic acid is qualitatively in good accord with our findings in solvent chlorobenzene; and, as we have already noted, their general conclusions accord with ours. However, a second-order kinetic form for addition of bromine is consistent with more than one rate-determining transition state. Consider the reaction sequences (a), (b), (c), (d), and (e), in which the assumed rate-limiting steps are identified by double headed arrows, and U stands for the unsaturated substance. For sequence (a), the transition state could be

(a) $U + Br_2 \rightarrow\!\!\!\rightarrow UBr^+ + Br^- \longrightarrow$ products

(b) $U + Br_2 \rightleftharpoons U,Br_2 \rightarrow\!\!\!\rightarrow UBr^+ + Br^- \longrightarrow$ products

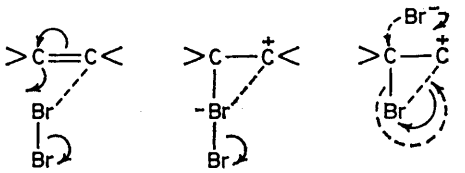
(c) $U + Br_2 \rightleftharpoons U,Br_2 \rightleftharpoons UBr^+ + Br^- \rightarrow\!\!\!\rightarrow$ products

(d) $U + Br_2 \rightleftharpoons U,Br_2 \rightleftharpoons [UBr^+Br^-] \rightarrow\!\!\!\rightarrow$ products

(e) $U + Br_2 \rightleftharpoons U,Br_2 \rightleftharpoons [UBr^+Br^-] \rightarrow\!\!\!\rightarrow [UBr^+Br^-]' \longrightarrow$ products

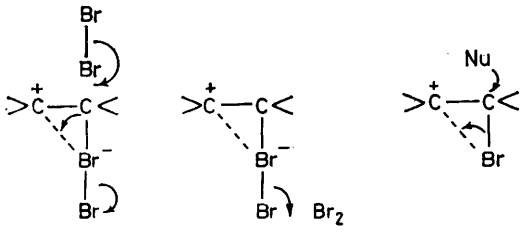
that represented in structure (7) [*cf.* (3)]. For sequence (b), structure (8) (with a more completely developed C–Br bond) is appropriate. For sequences (c) and (d), structure (9) would be more appropriate, the two alternative ways in which the new bonds could be developed being distinguished by solid and dotted curly arrows. For sequence (e), the rate-determining step is regarded as the internal reorganisation of an ion-pair intermediate.

The high values of ρ_I found in the present investigation seem to us to be better consistent with sequences like (a) and (b), in which the rate-determining stage is the heterolysis of a Br–Br bond, than with (c) or (d) in which the forming of the final bond to the nucleophile has become rate-determining. The influence of structural effects on sequence (e) could perhaps be similar to that on (a) or (b), both being primarily determined by structural effects on a pre-equilibrium between U and Br_2. Similar ambiguities exist in relation to transition states for third-order brominations.[22]



(7) (8) (9)

Products of Bromination.—(a) *With molecular bromine.* The products of these brominations of the 3β-substituted cholest-5-enes accorded with expectation from the literature. With molecular bromine under kinetic control in solvents deuteriochloroform, chlorobenzene, and acetic acid, 5α,6β-dibromides (accompanied in acetic acid by the appropriately substituted 6β-acetoxy-5α-bromocholestanes) were the only products. With 3β-trifluoroacetoxycholest-5-ene, which needed longer times for complete reaction, a little rearrangement to the 5β,6α-dibromide apparently supervened before work-up. 3α-Hydroxy- and 3α-methoxy-cholest-5-ene also gave 5α,6β-dibromides with bromine in deuteriochloroform. With these compounds, however, a substantial amount of a mixture of other, unidentified products was also formed, presumably by substitution perhaps involving neighbouring-group interaction with the hydroxy-group. These preparative reactions were carried out under conditions conducive to the third-order kinetic form ($-d[Br_2]/dt = k_3[\text{olefin}][Br_2]^2$). The reaction products do not help us to distinguish between a rate-determining transition state like (10) or one like (11). We believe,



(10) (11) (12)

because of the high ρ value for these third-order brominations, that the latter is more likely; the product-forming stage then becomes as in (12) (Nu = Br^- or HOAc), or some modification of this involving ion pairs.

[22] M. A. Wilson and P. D. Woodgate, *J.C.S. Perkin II*, 1976, 141.

A further matter not revealed by either the products or the kinetics is whether any of the 5α,6β-dibromide comes by way of electrophilic attack on the β-face of the double bond. Clearly, however, no detectable amount of α-acetoxy-β-bromo adduct arises from a product-determining stage having the stoicheiometry of (12) (Nu = HOAc); whereas acetic acid competes relatively effectively with bromide ion derived from the reagent in completing reaction on the β-face of the molecule and giving the 5α-bromo-6β-acetoxy-adduct. Similar competition between acetic acid and chloride ions is found for bromochlorination (see below).

(b) *With bromine acetate.* Preformed bromine acetate in chlorobenzene gives only the 5α-bromo-6β-acetoxy-adduct formed by α-attack and *anti*-addition. We now believe that bromine acetate,[23] like chlorine acetate,[1,24] behaves as a particularly effective donor of positive halogen which it provides as an entity of minimum effective size. The reaction sequence almost certainly involves the migration of OAc^- from one side of the plane of the attacked double bond to the other [*cf.* the sequences (a)—(e) for second-order brominations]. Even with this effectively small brominating agent, no product of β-bromination was found in the products.

(c) *With bromine chloride.* When 3β-trifluoroacetoxy cholest-5-ene was treated with bromine chloride in acetic acid containing a little sodium acetate, the mixture of products contained, as far as could be detected by ^1H n.m.r. spectroscopy, only the 5α-bromo-6β-chloro-adduct (65%) and the 5α-bromo-6β-acetoxy-adduct (35%). Reactions in deuteriochloroform (Table 1), however, gave more complex mixtures. The small amounts of 5α,6β-dibromides and dichlorides are probably derived from the formation of bromine and chlorine through disproportionation ($2BrCl \rightleftharpoons Br_2 + Cl_2$). These products are cut out entirely by the inclusion of tetraphenylarsonium chloride in the reaction mixture. We presume that the effect of added chloride ions is to catalyse a third-order (Ad_E3) bromochlorination.

The formation of a small proportion of 5α-chloro-6β-bromo-adduct could conceivably, in this complicated mixture of electrophiles and nucleophiles, have been derived by α-attack by electrophilic chlorine followed by nucleophilic capture of bromide. This is unlikely, however, since the same product in about the same proportion is formed in the presence of chloride ions. We think, therefore, that a ratio of *ca.* 70 : 3 represents the relative rates of formation of bromochloride by α- and β-attack by electrophilic bromine chloride.

5β,6α-Adducts were formed in these reactions also, in amounts which decreased from *ca.* 15 to *ca.* 3% as the 3β-substituent was changed from H to $CF_3{\cdot}CO_2$. These products did not arise by isomerisation of the 5α,6β-adducts, nor from the reactions with equilibrium amounts of bromine or of chlorine, as can be seen by comparison with the results for the former already quoted. They were in fact formed by a reaction in competition with the reaction catalysed by chloride ions, since they were cut out by the addition of chloride ions to the reaction mixture. There are two possible ways in which the diequatorial adducts could be produced. One is by electrophilic attack on the β-face of the steroid, followed by attachment of the nucleophile at the 6α-position with migration of the entering halogen to the 5β-position and inversion of the conformation of ring A. This mode of completion of the reaction might be expected, however, to be favoured by electron withdrawal from the reaction centre, since it is analogous to completion of reaction in the extended anti-Markownikoff sense, as in the formation [25] of $XCH_2{\cdot}CH(Hal){\cdot}CH_2(Nu)$ in competition with $XCH_2{\cdot}CH(Nu){\cdot}CH_2(Hal)$ from $XCH_2{\cdot}CH{:}CH_2$. The reverse is found in the present experiments; the results in Tables 1 and 2 establish that 5β,6α-adducts are formed in a proportion which diminishes with increasing electron withdrawal from the double bond. We conclude, therefore, that electrophilic attack on the α-face of the molecule can be followed, when chloride is the nucleophile, by attack at the 5β-position with conformational inversion of ring A. Such an ' extended Markownikoff-type ' addition would be expected to be diminished in importance by electron withdrawal from the double bond, as is observed.

That bromine chloride gives diequatorial products, whereas bromine does not, can be explained on steric grounds; chloride finds it easier to attach itself to the congested 5β-position than does bromide because of its smaller size.

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[25] P. B. D. de la Mare and J. G. Pritchard, *J. Chem. Soc.*, 1954, 3990.