Steroids and Walden Inversion. Part XXI. A Kinetic Study of the Acetolysis of* epi*Cholesteryl Bromide and Toluene*-p-*sulphonate.*

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A kinetic study of the acetolysis of *epi*cholesteryl toluene-*p*-sulphonate shows that the reaction is of the first order; the increased rate observed in the presence of added acetate ions is of the magnitude to be expected from an ionic-strength effect. An irreversible unimolecular heterolysis constitutes the rate-determining step and by the elimination of a proton from the resulting carbonium ion leads to cholesta-3 : 5-diene. The reaction is not catalysed by hydrogen ions and is unaffected by the presence of acetic anhydride.

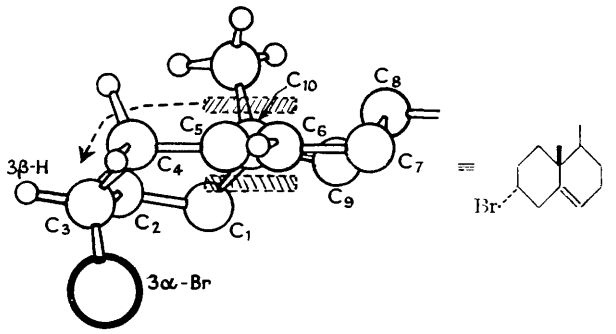
A similar kinetic study of the acetolysis of *epi*cholesteryl bromide furnished good first-order rate constants only in the presence of added acetate ions. In the absence of acetate ions the acetolysis displayed the same anomalous features as were observed previously in the case of cholesteryl bromide, showing autocatalytic characteristics and proceeding to an equilibrium. In the presence of acetic anhydride the rate was identical with the initial value of the rate for the uncatalysed reaction, which takes place by an irreversible unimolecular heterolysis and leads to the production of cholesta-3 : 5-diene.

As expected, the rates of acetolysis of the *epi*cholesteryl compounds are slower than those of the corresponding cholesteryl compounds; the ratio of the rates of acetolysis of the epimeric toluene-*p*-sulphonates is twice that for the epimeric bromides.

Kinetic studies of the acetolysis of cholesteryl toluene-*p*-sulphonate (Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838) and of cholesteryl bromide (Davies, Meecham, and Shoppee, preceding paper) have shown that both reactions involve a unimolecular heterolysis and that the π-electrons of the 5 : 6-double bond influence the kinetic and stereochemical

* Part XX, preceding paper.

course of the reaction. In view of the different configuration of molecules of the corresponding *epi*cholesteryl compounds, it was of interest to make a parallel kinetic study of their acetolysis. The configuration of the A and B rings of *epi*cholesteryl bromide is shown in the Figure. The carbon atoms $C_{(4)}$, $C_{(5)}$, $C_{(6)}$, $C_{(7)}$, and $C_{(10)}$ are coplanar and the bromine



atom possesses the axial conformation. It will be seen that the geometry of the system is unfavourable for interaction between the π-electrons of the 5 : 6-double bond and the β-face of $C_{(3)}$. For effective interaction, the π-electron cloud would have to operate over a distance approximately twice that involved in cholesteryl bromide and, in addition, the 4β-hydrogen atom will exert a screening effect. It follows that, by contrast with the cholesteryl compounds, the cation resulting by heterolysis of the bromine atom in *epi*-cholesteryl bromide will not be stabilised, and that the transition state of formation of the cation will therefore also not be stabilised, so that the energy of activation of the heterolysis will be increased and the rate decreased. In brief the 5 : 6-double bond will exert no significant " driving force " on the heterolysis and the *epi*cholesteryl derivatives should undergo acetolysis less readily than the corresponding cholesteryl compounds. Because of the relative instability of the 3α-yl cation its life will be shorter and it will be less likely to encounter an external anion; instead, the axial 4β-hydrogen atom is favourably disposed for elimination as a proton, leading to cholesta-3 : 5-diene. An alternative or competing process involves hydrogen shift from $C_{(4)}$ to $C_{(3)}$ to give the 4α-yl cation in which the positive charge is stabilised by delocalisation over the triad system $C_{(4)}$–$C_{(5)}$–$C_{(6)}$ (Evans and Shoppee, *J.*, 1953, 540; cf. Simonetta and Winstein, *J. Amer. Chem. Soc.*, 1954, **76**, 21, Fig. XVI). The above considerations imply that the acetolysis of *epi*-cholesteryl compounds should involve an irreversible heterolysis as the rate-determining step, the irreversibility arising from the rapid elimination of a proton from, or rearrangement of, the resulting cation.

TABLE 1. *Acetolysis of* epi*cholesteryl toluene*-p-*sulphonate.*

Concn. (10^{-2}M)	Added solute *	10^4k (min.$^{-1}$) (average)	Concn. (10^{-2}M)	Added solute	10^4k (min.$^{-1}$) (average)
	At 50·05°			*At* 50·05°	
1·725	0·0387M-acetate	21·3	1·739	None	15·3
1·737	0·0200M-acetate	19·5	1·731	0·0404M-NaOAc	19·9
1·738	0·0187M-TsO †	20·8	1·737	0·42M-H_2O	20·9
1·736	0·0393M-perchlorate	30·9	1·737	1·0M-Ac_2O	14·4
1·731	0·0176M-perchlorate + 0·0215M-$HClO_4$	23·9		*At* 40·25°	
			1·403	0·25M-H_2O	5·08
			0·881	0·25M-H_2O	5·25
			0·879	None	4·53

* Diphenylguanidinium salts. † TsO = toluene-*p*-sulphonate.

A summary of the results obtained from kinetic measurements on the acetolysis of *epi*cholesteryl toluene-*p*-sulphonate is given in Table 1. The molality given is that of the toluene-*p*-sulphonate. Each run was found to follow a first-order reaction and the specific rate constants, calculated by using the usual first-order rate expression, are also listed.

The increase in the rate in the presence of added acetate ions is of the order of magnitude

expected from an ionic-strength effect in acetic acid. Thus the two-fold increase in the concentration of added diphenylguanidinium acetate only increased the value of the specific rate constant from $19{\cdot}5 \times 10^{-4}$ to $21{\cdot}3 \times 10^{-4}$ min.$^{-1}$. The relatively greater increase in rate observed in the presence of diphenylguanidinium perchlorate may be attributed to the greater degree of dissociation of this solute. A unimolecular mechanism is therefore indicated and the rate-determining step must be the heterolysis of the *epi*-cholesteryl toluene-*p*-sulphonate. Since cholesta-3 : 5-diene forms the main product of acetolysis, the carbonium ion resulting from heterolysis is subsequently stabilised by elimination of a proton at $C_{(4)}$. The specific rate constant in the absence of added acetate ions showed little downward drift with time. Moreover, the addition of a common-ion solute such as diphenylguanidinium toluene-*p*-sulphonate produced no significant retardation of the reaction. These observations are consistent with the irreversibility of the rate-determining step.

Addition of water produced an increase in rate comparable with that observed from an ionic-strength effect. This again confirms the conclusion that the reaction involves an *E*1 mechanism. Increasing the dielectric constant of the solvent will tend to stabilise the charged transition state more than the neutral initial state and thus reduce the activation energy and accelerate the reaction. The reaction was not catalysed by hydrogen ions, and the presence of acetic anhydride led to only a very slight retardation.

The corresponding results obtained for the acetolysis of *epi*cholesteryl bromide in the presence of various solutes are given in Table 2.

In the absence of added acetate ions the acetolysis (Table 3) was found to display the same anomalous features as had been observed earlier for cholesteryl bromide (Davies, Meecham, and Shoppee, *loc. cit.*). The reaction shows autocatalytic characteristics and proceeds to an equilibrium corresponding to ~66% conversion.

Comparison of the initial specific rate constant obtained by extrapolation to zero time ($1{\cdot}07 \times 10^{-4}$ min.$^{-1}$) under these conditions with the specific rate constants given in Table 2.

TABLE 2. *Acetolysis of approx.* 0·02M-epi*cholesteryl bromide at* 94·8° ± 0·2°.

Added solute *	10^4k (min.$^{-1}$) (average)	Added solute	10^4k (min.$^{-1}$) (average)
0·0331M-acetate	1·30	0·0556M-NaOAc	1·51
0·0553M-acetate	1·78	1·0M-Ac_2O	1·07
0·0289M-acetate + 0·01120M-bromide	1·68	1·0M-Ac_2O at 106·6°	3·34
0·0339M-acetate + 0·0208M-perchlorate	2·32		

* Diphenylguanidinium salts.

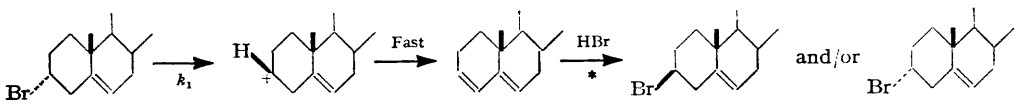
TABLE 3. *Acetolysis of approx.* 0·02M-epi*cholesteryl bromide at* 94·8° ± 0·2°.

Time (min.)	10^2M	Reaction (%)	10^4k (min.$^{-1}$)	Time (min.)	10^2M	Reaction (%)	10^4k (min.$^{-1}$)
240	2·13	3·5	1·50	1440	1·86	56·8	5·83
480	2·00	11·3	2·50	1920	2·02	61·7	4·99
720	2·03	30·3	5·01	2440	2·03	64·1	4·03
960	1·95	48·8	6·98				

shows that, apart from salt effects, the acetolysis of *epi*cholesteryl bromide also involves an *E*1 mechanism. The added salt effect is similar to, but smaller than, that observed for 1-phenylethyl chloride by Steigman and Hammett (*J. Amer. Chem. Soc.*, 1937, **59**, 2537). A small amount of reaction by an *E*2 mechanism would not be detected by our method, but the low nucleophilic power of the acetate ion renders this improbable. The rate in the presence of acetic anhydride is identical with that of the uncatalysed reaction. This behaviour is similar to that observed for the acetolysis of cholesteryl bromide and lends support to the view that the two reactions involve ionisation as the rate-determining steps. Addition of water to the solvent did not appreciably influence the autocatalysed reaction although at equilibrium the reaction was more complete.

The first four values in Table 3 can be fitted to a kinetic expression of the type that was found to apply to the acetolysis of cholesteryl bromide, but the last three values deviate

from this expression. Since the solutions developed colour as the reaction proceeded, it is unlikely that the titrations effected on solutions maintained at 95° for more than 24 hr. are very reliable. The apparent position of equilibrium is not only significantly less (66%) than that observed for cholesteryl bromide (85%), but is also inconsistent with the observation that addition of hydrogen bromide to cholesta-3 : 5-diene proceeds only to the extent of 10%. The annexed mechanism of reaction appears to account for the facts.



* 1 : 4-Addition to the diene is not excluded by the absorption ($\lambda_{max.}$ 210 mμ) observed.

TABLE 4.

	Cholesteryl toluene-*p*-sulphonate, 10^4k (min.$^{-1}$) at 50°	*epi*Cholesteryl toluene-*p*-sulphonate, 10^4k (min.$^{-1}$) at 50·05°	Cholesteryl bromide, 10^4k (min.$^{-1}$) at 94·8°	*epi*Cholesteryl bromide, 10^4k (min.$^{-1}$) at 94·8°
In presence of acetic acid	79	15·3	2·50	1·07
In presence of sodium acetate	200	19·9	7·0	1·51
E (kcal. mole^{-1})	25·0	25·2	26·5	26·8
$\Delta H^{\ddagger}$ (kcal. mole^{-1})	24·4	24·6	25·8	26·1
$\Delta S^{\ddagger}$ (kcal. mole^{-1} deg.$^{-1}$)	−1·0	−3·7	−13·5	−14·5

The data in Table 4 permit a comparison of the rates of acetolysis of cholesteryl and *epi*cholesteryl compounds. As expected, the rates of acetolysis of the *epi*cholesteryl compounds are slower. The ratio of rates of acetolysis of the toluene-*p*-sulphonates is twice that for the bromides. Acetolysis of the *epi*cholesteryl compounds is less sensitive to changes in the ionic strength of the solvent, as illustrated by the results given for approximately 0·05M-sodium acetate solutions. This observation is consistent with the smaller separation of charges in the transition state for a replacement reaction, compared with that for an elimination reaction. Correlation of the entropies of activation has already been made (Davies, Meecham, and Shoppee, *loc. cit.*).

EXPERIMENTAL.

For general experimental directions see preceding paper; ultra-violet absorption spectra were determined in EtOH on a Unicam S.P. 500 spectrophotometer with corrected scale.

epi*Cholesteryl Bromide and Toluene*-p-*sulphonate.*—The bromide was prepared according to Shoppee and Summers (*J.*, 1952, 1790) and the toluene-*p*-sulphonate by the method of Shoppee and Evans (*loc. cit.*).

The purification procedures for acetic acid, diphenylguanidine, and other reagents have been described by Davies, Meecham, and Shoppee (*loc. cit.*).

Kinetic Measurements.—The rate of acetolysis of *epi*cholesteryl bromide was studied at 94·8° ± 0·2° and at 106° ± 0·2°, the procedure described by Davies, Meecham, and Shoppee (*loc. cit.*) being used. The end-point in the titrations was always approached from the basic side, with crystal-violet as indicator. To obtain reproducible titration readings, it was necessary to match the colour at the end-point with that of a standard. Rate measurements on *epi*-cholesteryl toluene-*p*-sulphonate were made at 50·05° ± 0·01° and at 40·25° ± 0·01°. At these lower temperatures, since solvent loss is less significant and also toluene-*p*-sulphonic acid, unlike hydrogen bromide, is non-volatile in acetic acid solution, it was considered unnecessary to adopt the sealed-ampoule technique employed for measurements on the bromide. Instead, for each run, about 100 ml. of a solution of the toluene-*p*-sulphonate were made up by weight in a glass-stoppered flask. After a known weight of solvent had been allowed to attain the temperature of the thermostat, a weighed amount of the *epi*cholesteryl toluene-*p*-sulphonate was added. The flask was then shaken vigorously to ensure rapid dissolution of the solid; 10-ml. portions of the solution were withdrawn at appropriate intervals and the reaction stopped by rapid cooling. A 10-ml. portion from each run was weighed in order to correct for solvent expansion.

In the absence of added base, the solutions developed a brown colour after about 12 hours' immersion in the thermostat. Basic solutions on the other hand only coloured after 48 hr.

Analysis of Reaction Products.—*epi*Cholesteryl toluene-*p*-sulphonate (90 mg.) was dissolved in 10 ml. of 0·04M-diphenylguanidinium acetate solution in acetic acid. After immersion for 2 days in a thermostat at 50°, the solution was poured into water and extracted with benzene. The benzene extract was washed with water, 2N-sodium carbonate, and again with water, dried, and evaporated. An ethanolic solution of the residual oil showed $\lambda_{max.}$ 235 mμ corresponding to cholesta-3 : 5-diene, and the oil gave a violet colour in the Rosenheim test. Cholesta-3 : 5-diene, m. p. and mixed m. p. 77—78°, was the only product isolated when *epi*cholesteryl toluene-*p*-sulphonate was refluxed for 6 hr. with acetic acid in the presence or absence of diphenylguanidinium acetate.

An ampoule containing 48 mg. of *epi*cholesteryl bromide in 5 ml. of a 0·05M-diphenylguanidinium acetate solution in acetic acid was kept in a thermostat at 95° for 73 hr. The brown solution was poured into water and neutralised with sodium carbonate. The ether extract of the steroid products was washed with water, dried, and evaporated. The product, dissolved in pentane, was filtered through a column of aluminium oxide to remove diphenylguanidine present. The ultra-violet absorption spectrum of the resulting oil showed $\lambda_{max.}$ 235 mμ, corresponding to cholesta-3 : 5-diene. The oil gave a positive Beilstein test and so contained unchanged *epi*cholesteryl bromide. Similar results were obtained in the absence of diphenylguanidinium acetate. The ultra-violet absorption spectrum of the products showed, in addition to the maximum at 235 mμ, a slight maximum at 213 mμ, corresponding to an unconjugated Δ^4- or Δ^5-double bond.

A 0·02M-solution with respect to cholesta-3 : 5-diene and hydrogen bromide in acetic acid solution was kept at 106·6° for 7·5 hr. Titration of the remaining hydrogen bromide corresponded to 9·9% reaction. When the reaction was allowed to proceed for 44 hr. a 9·5% conversion was observed. The products gave a positive Beilstein test for bromine and showed a slight absorption maximum at 213 mμ, corresponding to an unconjugated Δ^4- or Δ^5-double bond.

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