[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. XIV. The 5,6-Double Bond in Cholesteryl *p*-Toluenesulfonate as a Neighboring Group

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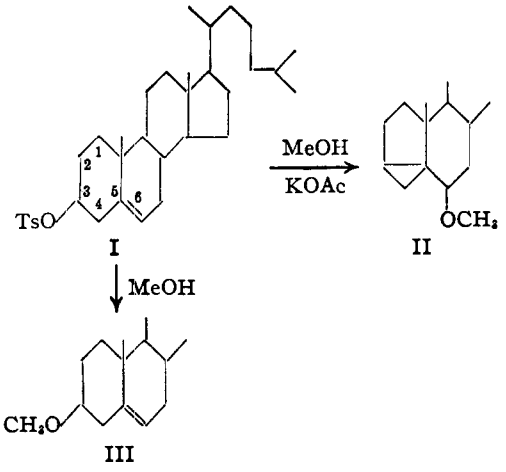
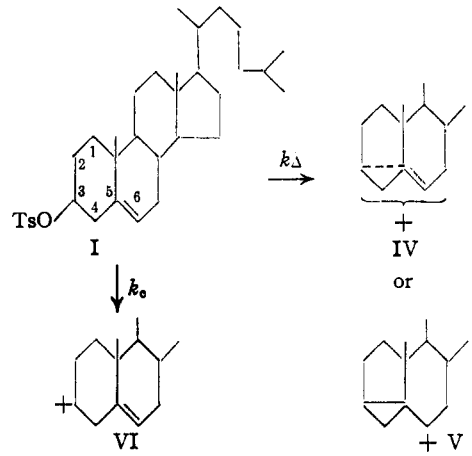
Shoppee[1] has very recently pointed out the tendency toward a steric result of retention of configuration in nucleophilic displacements at C_3 in Δ^5-cholestene derivatives and similar systems. Also he has drawn an analogy which we also have been using between this phenomenon and our work, presented in previous papers of this series, on participation of such neighboring groups as bromine in nucleophilic displacement processes. We are prompted to report the results of a study of the kinetics of acetolysis of cholesteryl *p*-toluenesulfonate I which we carried out some time ago as part of an investigation which was unavoidably interrupted.



It is known[2] that cholesteryl *p*-toluenesulfonate I on treatment with potassium acetate in methanol gives rise to a material which is best represented as the *i*-ether[3] II. In the absence of potassium acetate in the methanol, normal ether III is produced. By the action of potassium acetate in acetic anhydride, I is converted to *i*-acetate.[3c,d] Cholesteryl chloride, similarly to the toluenesulfonate, also[4] gives rise to *i*-ether. The *i*-ethers are relatively unstable, for example being converted to normal acetate on treatment with potassium acetate in glacial acetic acid.[3a,b] From the properties of the *i*-ethers it is apparent that the action of the potassium acetate in the methanol where *i*-ether is formed from I is merely to buffer the solution so that high acidity is not developed.

The *i*-sterol rearrangement (I → II) represents a case of participation in a nucleophilic displacement reaction by a properly situated ethylenic linkage, a suitable example of which we had been seeking for study when we began the present investigation. The most likely general mechanism for this rearrangement would seem to involve either the hybrid carbonium ion IV or the rearranged carbonium ion V. The intermediate (IV or V) then reacts with nucleophilic agents more rapidly at C_6 than C_3.



With regard to the formation of the intermediate IV or V, the alternatives (with no regard for stereochemistry) are a direct formation by ionization of I or prior formation of unrearranged carbonium ion VI, which then is converted to intermediate V (as though an energy barrier existed between V and VI). The specific reaction rate constants for the two modes of rate-determining ionization are symbolized by k_Δ and k_c, the symbols used previously[5] for other neighboring groups.

The kinetics of acetolysis of cholesteryl *p*-toluenesulfonate I support the general mechanism outlined and point to the direct ionization to intermediate IV or V (rate constant k_Δ). The acetolysis of I in glacial acetic acid proved to be very cleanly first-order, the first-order rate constants k at 35.00 and 50.00° being summarized in Table I.

The catalytic effect of water and sodium acetate on the acetolysis is quite marked. However, these effects are definitely solvent and ionic

(1) Shoppee, *J. Chem. Soc.*, 1147 (1946); journal received March 3, 1947.

(2) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).

(3) (a) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936); (b) Beynon, Heilbron and Spring, *ibid.*, 406 (1937); (c) Wallis, Fernholz and Gephardt, THIS JOURNAL, **59**, 137 (1937); (d) Ford and Wallis, *ibid.*, **59**, 1415 (1937); (e) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 1459 (1937); (f) Ford, Chakravorty and Wallis, THIS JOURNAL, **60**, 413 (1938); (g) Heilbron, Hodges and Spring, *J. Chem. Soc.*, 759 (1938); (h) Ladenburg, Chakravorty and Wallis, THIS JOURNAL, **61**, 3483 (1939).

(4) Wagner-Jauregg and Werner, *Z. physiol. Chem.*, **213**, 119 (1932).

(5) (a) Winstein, Grunwald and Ingraham, THIS JOURNAL, **70**, 821 (1948); (b) Winstein and Grunwald, *ibid.*, **70**, 828 (1948).

TABLE I

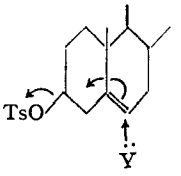
RATE CONSTANTS OF ACETOLYSIS k OF *ca.* 0.01 *M* CHOLESTERYL *p*-TOLUENESULFONATE IN GLACIAL ACETIC ACID

Other solute	Temp., °C.	$10^5 k$, min.$^{-1}$
.....	50.00	7.9[a]
0.50 *M* H_2O	50.00	12.2
.0100 *M* KOAc	50.00	19.8
.0100 *M* NaOAc	50.00	20.0
.0200 *M* NaOAc	50.00	20.0
.0100 *M* $LiClO_4$	50.00	24.1
.....	35.00	1.19[a]
.....	50.00	0.111[b]

[a] $\Delta H^{\ddagger}$ = 24.4 kcal./mole. [b] Cyclohexyl *p*-toluenesulfonate.

strength effects. Thus the effect of sodium acetate is not even as large as that of lithium perchlorate. Also raising the concentration of sodium acetate from 0.01 to 0.02 *M* gives no further increase in rate, which is not too surprising for ionic strength effects[6] in a solvent of as low a dielectric constant as that of acetic acid (*ca.* 6).

The fact that acetic acid is such a poor nucleophilic agent, that the rate is still nicely first order on addition of sodium acetate and that the effect of sodium acetate (the same at 0.01 and 0.02 *M*) is less even than that of lithium perchlorate indicates that the acetolysis represents a reaction of the



VII

unimolecular type and that concerted mechanisms of the type shown in VII are not important here.

The rate of acetolysis of cholesteryl *p*-toluenesulfonate I is seen to be some 10^2 (depending on ionic strength) times as large as that for cyclohexyl *p*-toluenesulfonate[7] also determined at 50.00° for comparison (Table I). The latter compound represents at least one good choice of a model substance for comparison in order to estimate k_6. Now reactivities of ring compounds are not yet clearly understood so that other comparisons are desirable. Actually, there are other indications of enhanced reactivity due to the 5,6-ethylenic linkage. Thus, Stoll[8] compared cholesteryl *p*-toluenesulfonate I with cholestanyl and ergostanyl *p*-toluenesulfonates in ethanol (no added ethoxide) at 78° and from his first-order rate constants one calculates factors of the order of 40 in favor of the cholesteryl ester. In the solvent ethanol we had felt there was more reason to suspect mechanisms of the type VII. However, the rate constant of acetolysis of cholesteryl *p*-toluenesulfonate I extrapolated to 78° is 0.176 min.$^{-1}$, a value nearly equal to Stoll's value of 0.18–0.19 min.$^{-1}$ in ethanol. Since ethanol and glacial acetic acid give comparable[9] solvolysis rates in unimolecular solvolyses, the indications are against mechanism VII in alcohol also. Further, in the case of chlorides, rather than toluenesulfonates, there are qualitative indications of greater reactivity of the Δ^5-compounds and Shoppee[1] refers to these.

The evidence then is that the 5,6-ethylenic linkage exerts a driving force[5] in favor of ionization of I, the main ionization being directly to intermediate IV or V (rate constant k_Δ). Thus a pair of electrons in an ethylenic linkage may play a role analogous to that of neighboring groups discussed in previous articles. There are further indications of the ionization by the k_Δ process. Thus the $\Delta H^{\ddagger}$ of activation for cholesteryl *p*-toluenesulfonate is less than that for the cyclohexyl ester[5a] by some 2.6 kcal./mole. This kind of a decrease with an increase in rate effected by a neighboring group has been noticed before.[5]

Also, the acetolysis of cholesteryl *p*-toluenesulfonate is much more sensitive to addition of water and salts than is the case with the cyclohexyl esters. While further comparison with medium effects in the case of higher molecular weight saturated esters such as cholestanyl are needed, one is led to compare the present situation with the one prevailing in the case of solvolysis of alkyl halides studied by Hughes, Ingold and co-workers.[6] In the latter case, the increase in rate by salt climbs as one proceeds from *t*-butyl to benzhydryl, separation of charge in the transition state being larger in the latter example. It is possible that the cyclohexyl-cholesteryl trend is analogous, the transition state for ionization of cholesteryl *p*-toluenesulfonate having positive charge both on C_3 and C_6.

Just as a pair of electrons of the 5,6 double bond in I imparts reactivity in ionization at C_3, the pair of electrons in the 3-membered rings of *i*-compounds such as II apparently imparts high reactivity at C_6. One very likely mechanism for the reverse *i*-sterol rearrangement of type II to type I, which we are also investigating, involves ionization followed by competitive reactions at C_3 and C_6. On this basis, judging by the high reactivity of *i*-compounds[3], V is not the intermediate. If these suppositions prove to be correct, the mesomeric ion IV would be the common intermediate for forward and reverse rearrangements, no energy barrier existing between the limiting resonance structures V and VI.

The over-all steric result of the conversion of cholesteryl *p*-toluenesulfonate I or chloride to an *i*-compound (type II) and back to a normal compound is clearly quite clean-cut retention of configuration. Thus, *i*-ether II gives cholesteryl

(6) Bateman, Church, Hughes, Ingold and Taher, *J. Chem. Soc.*, 979 (1940).

(7) Winstein, Grunwald, Buckles and Hanson, THIS JOURNAL, **70**, 816 (1948).

(8) Stoll, *Z. physiol. Chem.*, **246**, 6 (1937).

(9) Winstein, Hanson and Grunwald, THIS JOURNAL, **70**, 812 (1940).

chloride[3a,b] on treatment with hydrogen chloride in acetic acid and also is easily converted to cholesteryl acetate.[3a,b] This steric result is analogous to that involving other neighboring groups and is expected from the mechanism outlined for the formation of the *i*-compound and a reverse rearrangement which requires nucleophilic attack on C_3 to completely sever the C_3–C_5 bond.

Over-all retention of configuration with Δ^5-materials is very general and Shoppee[1] has summarized[10] the displacement reactions at C_3 in which 3-OH is converted to 3-Cl and 3-Cl to 3-OCOR. However, in these cases there is still need for further scrutiny to determine whether *i*-product is not the first predominant one, which quickly is rearranged to normal product.

Experimental

Materials.—Cholesteryl *p*-toluenesulfonate, m. p. 132–133°, was prepared in the usual manner.[3c] This material generated 98.5% of the theoretical amount of acid in acetolysis.

Lithium perchlorate trihydrate was prepared by treatment of Merck reagent grade lithium carbonate with perchloric acid. The reaction mixture, *p*H 4.5, was filtered, concentrated to a small volume and then allowed to cool slowly. The deposited crystals were pressed dry and dried in an oven at 140° for four hours. The hot liquid product was allowed to cool with stirring to yield a white crystalline solid, m. p. 93–94.5°.

The acetic acid solvent was prepared from Grasselli reagent grade acid and pure acetic anhydride, the residual concentration[5a] of the latter being 1×10^{-3} *M*.

Rate Measurements.—The titration procedures were those used previously.[5a] In case lithium perchlorate or sodium acetate (sodium carbonate was used) was added to the solvent, water was destroyed by treatment with the proper amount of acetic anhydride.

In the case of cyclohexyl *p*-toluenesulfonate,[7] m. p. 44–45°, sealed ampoules were used, concentrations being approximately 0.03 *M*. With the cholesteryl *p*-toluenesulfonate, concentrations approximately 0.01 *M* were used due to low solubility and low rate of solution. The toluenesulfonate was added to the solvent already at bath temperature and the mixture was shaken violently in a glass-stoppered flask until solution of the toluenesulfonate was nearly complete. Then the mixture was filtered rapidly into a volumetric flask already in the bath. In this way a homogeneous solution of the toluenesulfonate at bath temperature could be achieved in approximately five minutes. The initial concentration of the material was determined by titration of a sample of the reaction mixture after ten half-life periods.

Rates were followed to approximately 70% completion, the mean deviation of the individual first-order constants in one run being within 3% even for the rapid cases.

(10) Bergmann [*Helv. Chim. Acta*, **20**, 590 (1937)] previously had remarked on such anomalous steric results and ascribed them vaguely to the unsaturated linkage.

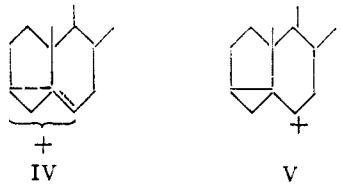
It is a pleasure to acknowledge helpful discussions with Drs. Byron Riegel of Northwestern University and Sam Siegel of the Illinois Institute of Technology.

Summary

A study of the acetolysis of cholesteryl *p*-toluenesulfonate has shown that the first-order rate constant is *ca.* 10^2 (because of a corresponding decrease in $\Delta H^{\ddagger}$) times that for the cyclohexyl ester. Also the rate is quite sensitive to the addition of water, sodium or potassium acetate, or lithium perchlorate to the acetic acid solvent.

The poor nucleophilic character of acetic acid, the fact that the salt effect of sodium acetate in acetolysis is no greater than that of lithium perchlorate, and the near identity of acetolysis and alcoholysis rates of cholesteryl *p*-toluenesulfonate speak against a mechanism for the isosterol rearrangement involving nucleophilic attack at C_6 in the rate-determining step. Thus the isosterol rearrangement represents a case of participation by a pair of electrons of the 5,6-ethylenic linkage in a unimolecular type displacement reaction at C_3.

The relatively high rates of acetolysis and alcoholysis of cholesteryl *p*-toluenesulfonate and other qualitative indications of high reactivity of Δ^5-materials show that the double bond furnishes a substantial driving force. This speaks for the direct formation of intermediate IV or V in the ionization of the C_3-derivatives. It is highly possible that the reversed isosterol rearrangement (*i*-compounds to normal ones) normally proceeds through the same intermediate. On this basis, the high reactivity of *i*-compounds speaks for a driving force due to the pair of electrons in the 3-membered ring and thus intermediate IV is indicated.



IV V

The over-all steric result of the conversion to an *i*-compound and back to a normal compound is analogous to the retention of configuration observed with other neighboring groups.

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