[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PRINCETON UNIVERSITY]

The Solvolysis of 4,4-Dimethylcholesteryl *p*-Toluenesulfonate. III. A Kinetic Study

WILLIAM J. A. VANDENHEUVEL, III,[1] ROBERT M. MORIARTY, AND EVERETT S. WALLIS

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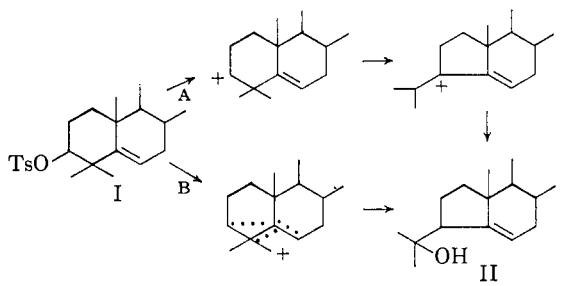
In order to determine the importance of homoallylic participation of the double bond in the solvolysis of 4,4-dimethylcholesteryl *p*-toluenesulfonate (I), the rate of hydrolysis of this compound was measured and compared with the rate of hydrolysis of 4,4-dimethylcholestanyl *p*-toluenesulfonate (VII). These values, taken with the values determined for cholesteryl and cholestanyl *p*-toluenesulfonates (IV and VIII, respectively), clearly indicate that participation plays an important role in this reaction, although the alcohol obtained from 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) is not the expected *i*-sterol but rather the ring-contracted alcohol 3-isopropanolyl-A-norcholest-5-ene (II).

In contrast to cholesteryl *p*-toluenesulfonate (IV), 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) does not undergo the "*i*-steroid rearrangement" yielding a 3,5-cyclo steroid. Under conditions which favor the rearrangement an alternate route is followed, namely, ring-contraction, resulting in the formation of 3-isopropanolyl-A-norcholest-5-ene (II). This result has been explained in terms of steric and electronic factors.[2a, b] The question of whether a homoallylic cationic intermediate was involved in this transformation could not be answered on the basis of product analysis alone. Two possible mechanisms are possible. Firstly, simple ionization followed by Wagner-Meerwein rearrangement (path A)[3] or, secondly, ionization assisted by the C-5:



C-6 double bond yielding a homoallylic cation (path B). It was felt that the two possible mechanisms could be distinguished by a kinetic study. If path A were correct, then the rate of solvolysis of 4,4-dimethylcholesteryl *p*-toluenesulfonate should resemble the rate of solvolysis of the saturated 4,4-dimethylcholestanyl *p*-toluenesulfonate. If path B were obtained, then participation of the C-5:C-6 double bond would be evidenced by a rate enhancement of the C-5:C-6 unsaturated compound compared to 4,4-dimethylcholestanyl *p*-toluenesulfonate. It may also be predicted that if this participation mechanism were operating the rate difference would be similar to the solvolytic rate difference between cholesteryl *p*-toluenesulfonate and cholestanyl *p*-toluenesulfonate. The results of this kinetic study in 9:1 dioxane-water (lithium acetate buffer) are given in Table I.

As can be seen, 4,4-dimethylcholesteryl *p*-toluenesulfonate solvolyzes approximately four times more readily than cholesteryl *p*-toluenesulfonate, whereas 4,4-dimethylcholestanyl *p*-toluenesulfonate solvolyzes at a rate only one-third greater than cholestanyl *p*-toluenesulfonate. These results are taken to indicate that 4,4-dimethylcholesteryl *p*-toluenesulfonate reacts *via* a homoallylic cation (participation of the double bond), the rate increase over cholesteryl *p*-toluenesulfonate being due to the methyl groups stabilizing the transition state electronically and possibly also due to operation of the Thorp-Ingold effect by which the geminal dimethyl group reduces the C-3:C-5 distance facilitating anchimeric assistance by the double bond. If the rate increase of 4,4-dimethylcholesteryl *p*-toluenesulfonate over cholesteryl *p*-toluenesulfonate were due to C-4:C-5 single bond participation, the rate of 4,4-dimethylcholestanyl *p*-toluenesulfonate (where such participation might be expected) should be significantly greater than that of cholestanyl *p*-toluenesulfonate, and such is not the case.

The observation that in the unsaturated esters the factor is only four (6-methylcholesteryl *p*-toluenesulfonate has been reported to solvolyze seventy-five times faster than cholesteryl *p*-toluenesulfonate[4]) indicates that the bulk of the C-4 methyl groups may reduce the solvation of the cation, and this reduction in solvation stabilization would, to a certain extent, mask any stabilization afforded by the geminal dimethyl group via the above-mentioned effects. In addition, 4,4-dimethylcholesteryl *p*-toluenesulfonate has a meta axial interaction between the C-10 methyl group and the

(1) Merck Fellow, 1958–1959.

(2) (a) R. M. Moriarty and E. S. Wallis, *J. Org. Chem.*, **24**, 1074 (1959). (b) R. M. Moriarty and E. S. Wallis, *J. Org. Chem.*, **24**, 1987 (1959). The flow chart in this reference (Part II of this series) is in error. The structural formula labeled II should be 4,4-dimethyl-3,5-cyclocholestan-6β-ol; the structural formula labeled III should be 3-isopropanolyl-A-norcholest-5-ene [called 3-(2-hydroxy-2-propyl)-A-norcholest-5-ene in this reference].

(3) Y. M. Y. Haddad and G. H. R. Summers, *J. Chem. Soc.*, 769 (1959).

(4) R. A. Sneen, *J. Am. Chem. Soc.*, **80**, 3982 (1958).

TABLE I[a]

Compound	Rate, k_1 Sec.$^{-1}$		
	50.0 ± 0.1°	75.0 ± 0.1°	100.0 ± 0.1°
4,4-Dimethylcholesteryl *p*-toluenesulfonate	9.13×10^{-5}	1.26×10^{-3}	1.10×10^{-2}[b]
Cholesteryl *p*-toluenesulfonate	2.27×10^{-5}	3.24×10^{-4}	2.72×10^{-3}
4,4-Dimethylcholestanyl *p*-toluenesulfonate			6.10×10^{-5}
Cholestanyl *p*-toluenesulfonate			4.64×10^{-5}

[a] The values given are the averages of several determinations. [b] Extrapolated from the values at the lower temperatures.

axial C-4 methyl group, and in order to relieve this interaction the A-ring might become somewhat distorted, resulting in a geometry in which less effective overlap of the π-orbitals of the double bond with the developing empty *p*-orbital at C-3 during ionization might occur.

In conclusion it may be said that 4,4-dimethylcholesteryl *p*-toluenesulfonate reacts predominantly *via* C-5:C-6 double bond participation. Further work is called for to determine the path followed in the solvolysis of 4,4-dimethylcholestanyl *p*-toluenesulfonate.

EXPERIMENTAL[5]

4,4-Dimethylcholesteryl p-toluenesulfonate (I).[2a]

Cholesteryl p-toluenesulfonate (IV). Cholesterol and *p*-toluenesulfonyl chloride were allowed to react in pyridine according to the procedure utilized for the preparation of I to give IV (69%), m.p. 131.5–133°; reported 131.5–132.5°.[6]

4,4-Dimethylcholestanyl p-toluenesulfonate (VII). 4,4-Dimethylcholestanol and *p*-toluenesulfonyl chloride were treated in pyridine at room temperature for 18 hr. After this period the reaction mixture was poured into ice water, stirred, and then extracted with ether three times. The combined organic layers were washed successively with cold 1:1 hydrochloric acid and water, dried, and filtered. Treatment with decolorizing charcoal followed by filtration and crystallization yielded VII (65%), m.p. 108–109°.

Anal. Calcd. for $C_{36}H_{58}O_3S$: C, 75.74; H, 10.24. Found: C, 75.51; H, 10.20.

Cholestanyl p-toluenesulfonate (VIII). Cholestanol and *p*-toluenesulfonyl chloride were allowed to react in pyridine as in the preparation of VII above. Crystallization from ether yielded VIII (34%), m.p. 132.5–133.5°; reported 134–135°.[7]

Anal. Calcd. for $C_{34}H_{54}O_3S$: C, 75.23; H, 10.03; S, 5.90. Found: C, 75.09; H, 9.91; S, 5.76.

Determination of the rates of hydrolysis. The rates of hydrolysis were followed by titration of aliquots (in sealed ampoules) of the approximately $1 \times 10^{-2}M$ ester solutions with standard base after appropriate time intervals. In the cases of cholesteryl *p*-toluenesulfonate and 4,4-dimethylcholesteryl *p*-toluenesulfonate, the theoretical infinity titration volumes were used in the calculation of the rate.

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PRINCETON, N. J.

(5) Melting points (capillary) are uncorrected; analyses by George Robertson, Florham Park, N. J., and Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

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(7) A. Stoll, *Z. physiol. chem.*, **207**, 147 (1932).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Thermodynamic Properties of Activation for *cis*- and *trans*-Deoxymercuration[1]

MAURICE M. KREEVOY, JOHN W. GILJE, LEROY T. DITSCH, WADIM BATOREWICZ, AND MARGARET A. TURNER

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Entropies (ΔS^*) and enthalpies (ΔH^*) of activation have been measured for four additional deoxymercuration reactions induced by nonhalogen acids. These have been compared with values previously obtained for cyclohexane derivatives and with each other. Variations in ΔH^* and ΔS^* are semiquantitatively predicted by theory if the curve of potential energy *vs.* θ has deep minima at *both* 0° and 180° and maxima at 90° and 270°. (The angle between the carbon-carbon-oxygen plane and the carbon-carbon-mercury plane is θ.) This is a reasonable result in view of the likely mechanism for deoxymercuration.

In previous papers[2-4] the mechanism of the acid induced deoxymercuration reaction (Equation 1) has been discussed, and it has been shown that the preferred conformation of the transition state is *trans*.[3] It is possible, however, to prepare five- and six-membered cyclic oxymercurials in

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(4) M. M. Kreevoy, L. L. Schaleger, and J. C. Wave, unpublished work.

(5) J. Romeyn and G. F. Wright, *J. Am. Chem. Soc.*, **69**, 697 (1947); it is assumed that the structures assigned in ref. 3 are correct.