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THE EFFECT OF REMOTE SUBSTITUENTS UPON THE COURSE AND REACTIVITY OF HOMOALLYLIC SYSTEMS

THE SOLVOLYSIS OF 19-SUBSTITUTED CHOLESTERYL *p*-TOLUENESULPHONATE ESTERS

R. M. MORIARTY and T. D. J. D'SILVA[1]
Chemistry Department, The Catholic University of America, Washington

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Abstract—Several C_{19} substituted cholesteryl *p*-toluenesulphonate esters have been synthesized for the purpose of studying the effects of the C_{19} substituent upon the course and rate of solvolytic reactions in this system. The rates of acetolysis were determined for the C_{19} hydroxy, methoxy, acetoxy, aldehydo and thioacetal cholesteryl *p*-toluenesulphonates. Kinetic evidence is presented for transannular stabilization of the transition state for ionization possibly *via* C_6–C_{19} bridged structures. The relative magnitudes of the rate variations are discussed in terms of inductive effects, ring strain effects incurred in the bridged structures and entropy factors.

Solvolysis of Δ^5-cholestene-3β, 19-diol 3-*p*-toluenesulphonate (IX) does not yield 3α, 5-cyclo-6β, 19-oxidocholestane (XIII), the product corresponding to intramolecular neutralization of the ion. The fact that the predominant product is 3α, 5-cyclocholestane-6β, 19-diol (XII), indicates that in spite of a kinetically demonstrable interaction between C_6–C_{19}, the stereochemistry of attack of solvent at C_6 is not influenced by such an effect. Similarly, hydrolysis of Δ^5-cholestene-3β-ol-19-al 3-*p*-toluenesulphonate (VIII) yielded mainly 3α, 5-cyclocholestane-6β-ol-19-al (XIV). The mechanistic implications of these results discussed along with the general question of the possible modes of interaction of remote polar groups with developing cationic centres in solvolytic reactions.

Remote substituents within a molecule may influence reactivity at a distant centre by either a steric or polar mechanism. Steric effects in this context differ in kind from those which hinder the approach of either solvent or an attacking reagent in the immediate vicinity of the reaction centre. For example, Barton *et al.*[2] have demonstrated convincingly the effect of structural changes at large distances from the centre of reactivity upon the relative rate of aldol condensation in certain steroidal and triterpenoid examples. Remote polar substituents may affect reactivity by an electronic interaction transmitted either through the connecting atoms or through the interannular space. Both of these effects are correlatable by linear free energy functions.[3,4] Positive deviations from such relationships are diagnostic of either

[1] Submitted in partial fulfillment of the requirements for the Ph.D., 1964.
[2] D. H. R. Barton, F. McCapra, P. J. May and F. Thudium, *J. Chem. Soc.* 1297 (1960).
[3] R. W. Taft Jr., [a] *J. Amer. Chem. Soc.* 74, 2729 (1952); [b] 74, 3120 (1952); [c] 75, 4231 (1953); [d] 75, 4534 (1953); [e] 75, 4538 (1953).
[4] J. D. Roberts and W. T. Moreland, *J. Amer. Chem. Soc.* 75, 2167 (1953).

anchimeric assistance or steric effects which favour the change involved in the reaction. Examples of remarkably large effects of polar substituents at large distances from the reaction centre have been presented by Peterson[5] and Schwarz *et al.*[6] The rate of addition of trifluoroacetic acid to olefins was shown to be affected significantly by substituents removed by four carbon atoms from the olefinic group. Schwarz *et al.*[6] have found that the rate of bromine addition to the C_5–C_6 double bond of androstene derivatives was simultaneously and independently influenced by the nature of the C_3 and C_{17} substituents. Remote substituents have been shown to affect the relative acid strengths of 4-substituted bicyclo [2,2,2]-octane-1-carboxylic acids[4] and the rates of addition of 2,4-dinitrobenzenesulphenyl chloride to substituted cyclohexenes and norbornenes.[7] Long range electrostatic interactions also play a key role in biochemical systems where both conformation and reactivity may be controlled by remote charged groups.[8] Johnson has proposed that the high nucleophilic reactivity of the double bond in isopentenyl pyrophosphate may result from a polarization effect exerted by the neighboring pyrophosphate group.[9] Cornforth has also discussed this possibility.[10]

It was felt that the unique stereochemical and electronic features present in the homoallylic 3β-tosyloxy-Δ^5-C_{19}-substituted steroids offered a potentially useful substrate for the purpose of gaining further information about the effect of transannular polar groups in solvolytic reactions. Since the A and B rings of these compounds are held rigidly in place, fairly accurate values of internuclear distances are obtainable. Also the general arrangement of a polar group held over a highly polarizable double bond bears significant affinity with the situation obtaining in enzymatic systems where a polar group exerts an influence through a cavity of low dielectric constant upon a reactive centre. Finally, from a practical point of view, synthesis of the required compounds, measurement of solvolytic rates, and product analysis were considered to be reasonably straightforward.

It is known that the solvolysis of cholesteryl *p*-toluenesulphonate is accompanied by participation of the C_5–C_6 double bond in the rate limiting ionization step.[11] Such participation is evidenced by substantial rate acceleration over the analog without the homoallylic double bond. Delocalization of the π-electrons of the double bond towards the developing *p*-orbital at C_3 causes accumulation of positive charge at C_6. A substituent at C_{19} might stabilize this positive centre by either direct nucleophilic participation as symbolized by A → B, or by a comparatively weaker field stabilization. The essential difference between these two modes of interaction depends upon the

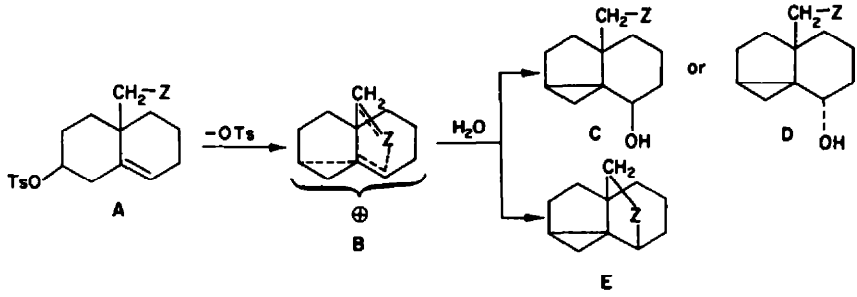
[5a] P. E. Peterson and G. Allen, *J. Org. Chem.* **27**, 2290 (1962);
[b] P. E. Peterson and G. Allen, *J. Amer. Chem. Soc.* **85**, 3608 (1963).
[6a] V. Schwarz, S. Hermanek and J. Trojanek, *Chem & Ind.* 1212 (1960);
[b] V. Schwarz, S. Hermanek and J. Trojanek, *Coll. Czech. Chem. Comm.* **26**, 1483 (1960);
[c] V. Schwarz and S. Hermanek, *Tetrahedron Letters* 809 (1962);
[d] for an extension of the interpretation of the conclusions reached in the above papers see P. E. Peterson, *Tetrahedron Letters* 181 (1963).
[7] H. Kwart and L. J. Miller, *J. Amer. Chem. Soc.* **83**, 4552 (1961).
[8] For examples see E. M. Kosower, *Molecular Biochemistry* pp. 216–219. McGraw-Hill, New York (1962).
[9] W. S. Johnson and R. A. Bell, *Tetrahedron Letters* No. 12, 27 (1960).
[10] J. W. Cornforth, *International Symposium on the Chemistry of Natural Products* Butterworth, p. 619. London (1961).
[11] S. Winstein and E. M. Kosower, *J. Amer. Chem. Soc.* **81**, 4399 (1959) and Refs contained therein.

distance between the C_{19} atom, Z, and the potential cationic centre at C_6. The coulombic interaction between charges separated by a few atomic diameters is given by

$$E(\text{kcal/mole}) = 333q_1q_2 \frac{(\text{in fractions of unit charges}).}{Dr\ (\text{in Å})}$$

Furthermore, the magnitude of C_6–C_{19} transannular interaction would vary with the covalent radius and nucleophilicity of Z. In the case of Z = nitrogen or oxygen, overlap of a p lobe on Z with the developing p orbital at C_6 might be envisioned. Sulphur would be particularly effective in this type of interaction due to its relatively large covalent radius. Operation of such transannular stabilization should be evidenced by a solvolytic rate enhancement for the C_{19} substituted derivative over cholesteryl *p*-toluenesulphonate. Thus, in addition to the normal homoallylic participation, a further stabilization would be superimposed resulting in a lowering of the activation energy for achieving the transition state. In the absence of such a stabilization, the principal effect of the C_{19} polar substituents would be a negative inductive effect transmitted through the σ bond network, and the result of this interaction would be a destabilization of the transition state for ionization. This would be reflected by a rate retardation.

The extent of bond formation between C_6 and C_{19} should, in principle, be determined by the configuration of the newly created asymmetric centre at C_6; i.e., in the absence of C_6–C_{19} participation, attack by solvent would give the β and axial C_6 substituted cyclosterol.[11] Participation of the type indicated by structure B might lead to intramolecular neutralization (B → E) or, alternatively, bimolecular coordination with solvent might yield the stereochemistry resulting from back side opening of the bridged intermediate (B → D).

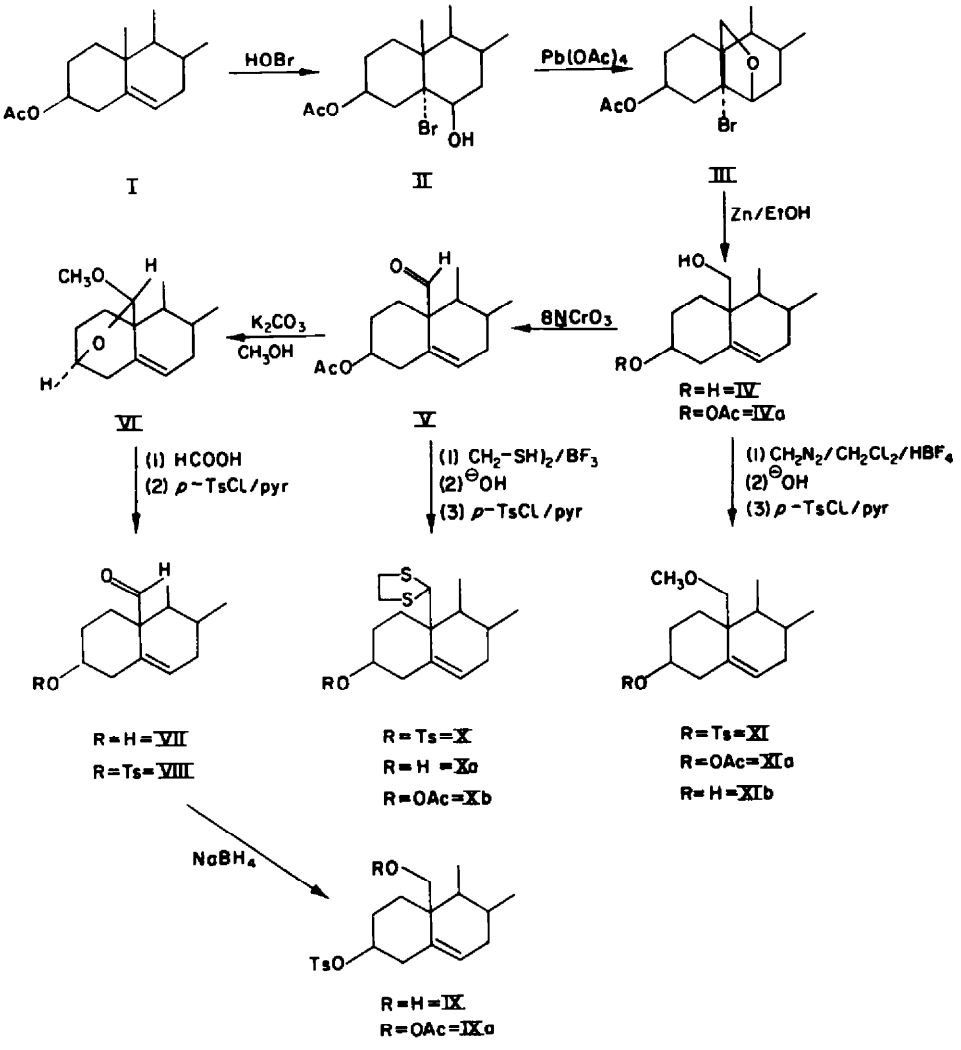


The synthesis of compounds of the general formula A proceeded from cholesteryl acetate (I) *via* conversion to 5α-bromocholestane-3β, 6β-diol 3-acetate (II) followed by lead tetraacetate oxidation[12] in the presence of iodine[13] to 6β, 19-oxido-5α-bromocholestane-3β-ol-3-acetate (III). Treatment of III with zinc in ethanol resulted in smooth debromination to Δ^5-cholestene-3β, 19-diol 3-acetate (IVa). Saponification of IVa yielded the corresponding diol, Δ^5-cholestene-3β, 19-diol (IV), which failed to undergo selective monotosylation at C_3. In order to obtain the desired Δ^5-cholestene-3β, 19-diol 3-*p*-toluenesulphonate (IX), it was necessary first to oxidize Δ^5-cholestene-3β, 19-diol 3-acetate (IVa) to the corresponding C_{19} aldehyde, Δ^5-cholestene-3β-ol-19-al

[12a] A. Bowers, L. C. Ibanez, M. E. Cabezas and H. J. Ringold, *Chem. and Inc.* 1299 (1960);
[b] A. Bowers, E. Denot, L. C. Ibanez, M. E. Cabezas and H. J. Ringold, *J. Org. Chem.* **27**, 1862 (1962).
[13a] J. Kalvoda, K. Heusler, G. Anner and A. Wettstein, *Helv. Chim. Acta* **46**, 618 (1963);
[b] J. Kalvoda, U. Ueberwasser, G. Anner and A. Wettstein, *Ibid.* **46**, 1361 (1963).

3-acetate (V). Saponification of V ultimately yielded the corresponding alcohol along with the intramolecular acetal (VI). Tosylation of VII yielded Δ^5-cholestene-3β-ol-19-al 3-*p*-toluenesulphonate (VIII) which could be reduced with sodium borohydride at 0° to Δ^5-cholestene-3β, 19-diol 3-*p*-toluenesulphonate (IX). Acetylation afforded Δ^5-cholestene-3β, 19-diol 3-*p*-toluenesulphonate-19 acetate (XIa). Treatment of Δ^5-cholestene-3β-ol-19-al 3-acetate (IIIa) with ethane dithiol and boron trifluoride etherate yielded the C_{19}-thioacetal which was converted to Δ^5-cholestene-3β-ol-19-al 3-*p*-toluenesulphonate-19-dithioethaneacetal (X). Conversion of IVa to the C_{19}-methyl ether was accomplished by treatment of IVa with diazomethane and fluoroboric acid in methylene chloride. Tosylation of the derived alcohol yielded Δ-cholestene-3β, 19-diol 3-*p*-toluenesulphonate 19-methylether (XI).

The structure of the key compound, Δ^5-cholestene-3β, 19-diol 3-acetate (IVa), has been established previously.[14] Compounds V–XI, which are derived from IVa,



[14] R. M. Moriarty and T. D. D'Silva, *J. Org. Chem.* **28**, 2445 (1963).

were characterized on the basis of method of preparation, elemental analysis, IR and NMR spectra. NMR results and IR absorption spectral data are presented in the Experimental section.

RESULTS AND DISCUSSION

First order rate constants for acetolysis and activation parameters for the various C_{19} substituted cholesteryl *p*-toluenesulphonate esters are collected in Table 1. The first obvious fact revealed by these results in the occurrence of significant homoallylic participation by the C_5–C_6 double bond. The rate of acetolysis at 50·0° of Δ^5-cholestene-3β, 19-diol 3-*p*-toluenesulphonate (IX) is 230 times faster than cholestanyl *p*-toluenesulphonate and about twice as fast as cholesteryl *p*-toluenesulphonate. Similarly Δ^5-cholestene-3β, 19-diol 3-*p*-toluenesulphonate-19-methyl ether (XI) solvolyses 2·4 times faster than cholesteryl *p*-toluenesulphonate. Presence of the larger and more highly polarizable sulphur at C_{19} leads to a substantially bigger effect, i.e., the C_{19}-thioacetal compound, X, displays a rate of acetolysis which is 1000× faster than cholestanyl *p*-toluenesulphonate and 10 times faster than cholesteryl *p*-toluenesulphonate. The most significant quantity of concern here is the ratio of rates of the C_{19} substituted compounds to cholesteryl *p*-toluenesulphonate. The rate increase relative to cholesteryl *p*-toluenesulphonate represents the additional effect due to the C_{19}-substituent. Only the C_{19} acetoxy and C_{19} aldehydo derivatives, IXa and VIII, solvolyse more slowly than cholesteryl *p*-toluenesulphonate.

A logical interpretation of these results requires some estimate of the inductive retardation of the substituents upon the homoallylic ion. Although the Taft relationship[15], $\log k/k_0 = \sigma^*\rho^*$, has not been applied to such homoallylic systems[16] a very

TABLE 1. FIRST ORDER RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE ACETOLYSIS OF C_{19}-SUBSTITUTED CHOLESTERYL *p*-TOLUENESULPHONATES[a]

3-*p*-Toluenesulphonate	$T°$	k (sec^{-1}) × 10^5	Ea kcal/mole	$\Delta H‡$ kcal/mole	$\Delta S‡$ e.u.
Cholestanyl	50·2°	0·108			
Cholesteryl	50·2°	12·7	25	24·4	−1·0
Δ^5-Cholestene-3β	34·8°	4·17	23·8	22·0	−7·4
19-diol (IX)			±0·5	±0·9	±3·0
	50·2°	24·5			
	70·5°	223			
Δ^5-Cholestene-3β-ol-19-al	50·2°	0·584	25·3	24·8	−6·3
(VIII)	58·6	1·58			±2·0
	70·5°	5·85			
Δ^5-Cholestene -3β,19-diol	42·7°	4·50	22·2	21·5	−10·8
19-acetate (IXa)	50·2°	10·3			±2·5
	70·5°	77·3			
Δ^5-Cholestene-3β-ol-19-al	34·8°	22·7	22·3	21·6	−7·5
19-ethane dithioacetal (X)	42·7°	41·7	±0·5	±0·5	±1·5
	50·2°	127			
Δ^5-Cholestene-3β,19-diol	50·2°	29·9			
19-methyl ether (XI)					

[a] Rates were determined titrimetrically and all compounds in the series showed good first order behaviour.

[15] R. W. Taft, Jr., *J. Amer. Chem. Soc.* **74**, 4231 (1953).

[16] R. A. Sneen, *J. Amer. Chem. Soc.* **80**, 3982 (1958). The Hammett relationship has been applied in the treatment of the relative rates of solvolysis of *p*-substituted 6-aryl cholesteryl *p*-toluenesulphonates.

approximate value for the effect of the C_{19} substituents upon the rate of solvolysis is calculable. If we assume that the C_{19} substituent exerts only a negative inductive effect upon the formation of the homoallylic ion, a choice must be made concerning the mode of transmission of the effect. If it is transmitted through the intervening carbon-carbon bonds, it would act principally at C_5 and C_6 since these are the centres of the homoallylic ion nearest the C_{19} carbon. A potentially more important effect,[17] however, is the dipolar interactions across space between the departing tosylate anion and the positive end of the dipole of the C_{19} substituent. Quantitative evaluation of this effect is difficult due to the unknown conformational orientation of the C_{19} substituent with respect to the C_3 tosyloxy group. The simplified and admittedly crude calculations which we have applied to this system uses the substituent constant σ^* for the C_{19} substituent and a transmission coefficient of 0·50 for attenuation of the inductive effect due to the intervening carbon atom at C_{10}. Calculated and observed rate constants based upon these considerations are presented in Table 2. Assuming

TABLE 2. CALCULATED AND OBSERVED EFFECTS OF C_{19} SUBSTITUENTS

3-*p*-OTs	$\sigma^*\rho^*(0{\cdot}5)^{a,b}$	kx/kH[c] calc.	kx/kH obs.	kx obs./kx calc.
Δ^5-Cholestene-3β, 19-diol (IX)	−0·97	0·11	1·9	18
Δ^5-Cholestene-3β, 19-diol 3-acetate (IXa)	−1·74	0·018	0·8	45
Δ^5-Cholestene-3β 19-diol 3-methyl ether (XI)	−0·91	0·12	2·5	21

[a] Assuming $\rho^* = -3{\cdot}49$[18a,b] Transmission coefficient = 0·50[19] kH refers to cholesteryl *p*-toluenesulphonate.[c]

that steric acceleration is not operative i.e., raising of the ground state energy due to the steric effect of the C_{19} substituent, the implication of a rate accelerating polar interaction between C_6 and C_{19} seems inescapable. The exact nature of the stabilization cannot be more closely defined. The phenomenon could be considered also as a form of intramolecular solvation of the ion by the polar groups. Just as polar solvents stabilize charge development in the transition state of reactions involving charge creation, the C_{19} polar substitution could serve a similar function. The role of changes in polymolecular solvation of the ground state and transition state which might be caused by the polar C_{19} substituent also represents a factor of potential but unassessable importance.

An alternative description of this unusual form of anchimeric assistance may be formulated. The C_{19} substituent may be thought of as exerting a transannular stabilizing effect upon developing positive charger at C_6 in the rate determining ionization step, or alternatively, one might consider the C_{19} group as a neighbouring group which exerts anchimeric assistance for solvolysis transmitted to C_3 through the olefinic linkage over the C_3–C_5 distances. In this sense the observed effect is formally related to the phenomenon of homoallylic transmission discussed by Sneen.[18]

[17] We wish to thank the referee for pointing this out to us.

[18a] Values of σ^* are taken from R. W. Taft, *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) p. 395. J. Wiley, New York, N.Y. (1956);

[b] ρ^* of −3·49 is taken from A. Streitwieser, Jr., *J. Amer. Chem. Soc.* **78**, 4935 (1956).

Although the C_{19} acetoxy derivative is slightly slower than cholesteryl *p*-toluenesulphonate, reference to Table 2 reveals that the observed rate is larger by a factor of 45 than that expected upon the basis of electron withdrawal. Further reference to Table 2 reveals that the acceleration shown by the C_{19} acetoxy compound is twice as large as that of either the methoxy or hydroxy. This is particularly striking when one considers that a C_6–C_{19} bridged structure involving the acetoxy carbonyl is somewhat unfavoured due to the necessity of a seven-membered ring structure. Participation of the alkyl oxygen is unfavoured due to the partial delocalization of electrons on oxygen into the carbonyl group to give the usual ester resonance structure. The rates of acetolysis of the C_{19} hydroxy, acetoxy, methoxy and ethane dithioacetal all proceed with relatively large negative entropies of activation. This trend is in agreement with the expected high degree of order possessed by the suggested bridged structures. However, such entropy changes may also be associated with changes in solvation of the ground state relative to the transition state.

The slow rate of solvolysis of the Δ^5-cholestene-3β-ol-19-al 3-*p*-toluenesulphonate (VIII) probably results from the rate retarding inductive effect of the aldehydo group uncompensated by incursion of a stabilizing bridged structure. The positive end of the carbonyl dipole would be expected to oppose the development of positive charge at C_6.[20] Baddely *et al.*[21] have postulated bridged structures involving the aldehydo group in displacement in the decalin series. The absence of bridged aldehydo structures in our system may be associated with the inability of acetic acid to add to carbonyl to form an ortho ester type intermediate. This is due both to the low nucleophilicity of acetic acid and the steric overcrowding which would exist in such a structure.

In the case of the C_{19} hydroxyl compound a relatively strong intramolecular hydrogen bond exists between the C_5–C_6 π-electrons and the primary hydroxyl group.[22] This clearly indicates the steric possibility of interaction between these two centres, however, such an association would in fact lead to a rate decrease since the π-electrons would be somewhat less available for delocalization towards C_3 in the ionization step. One further rather subtle but potentially important steric effect should also be taken into account in this system. As the molecule approaches the transition state for ionization, partial formation of a C_3–C_5 bond would tend to decrease the interaction of the C_{19}-hydroxyl group and the C_6 cationic centre. This is a consequence of: (a) the increased C_6–C_{19} distance resulting from the deformation of the A ring in the C_3–C_5 cyclosterol structure (inspection of Dreiding models of ions A and B reveals C_6–C_{19} oxygen–carbon distances of 2·8 Å and 3·2 Å, respectively); and (b) the steric strain associated with the *trans* annelation of two five membered rings.[23] This latter consideration is also pertinent in a discussion of the products formed in

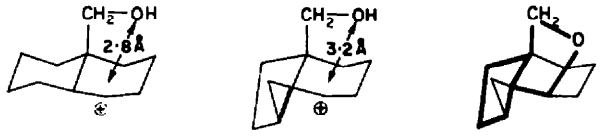
[19] J. C. McGowan, *J. Appl. Chem.* **10**, 312 (1960).

[20] For an excellent discussion of such dipolar opposition effects see K. Wiberg, *Physical Organic Chemistry* pp. 282–285. J. Wiley, New York, N.Y. (1964).

[21a] G. Baddeley, E. K. Bayles and B. G. Heaton, *Proc. Chem. Soc.* 451 (1961);
[b] G. Baddeley, G. G. Heaton and J. W. Rasburn, *J. Chem. Soc.* 3828, 3835 (1961).

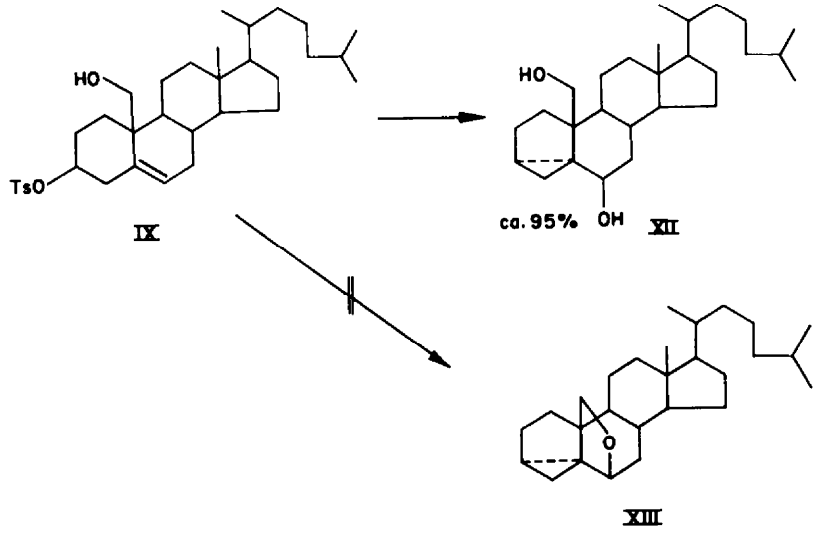
[22] We wish to thank Dr. T. S. S. Murty, Princeton University for this determination. Δ^5-cholestene-3β-19-diol 3-acetate (IV) showed absorption at 3635 cm^{-1} (free) and 3582 cm^{-1} (bonded), $\Delta\nu$ 53 cm^{-1}; Δ^5-cholestene-3β, 19-diol 3-*p*-toluenesulphonate (X) showed absorption at 3635 cm^{-1} (free) and 3584 cm^{-1} (bonded), $\Delta\nu$ 51 cm^{-1}.

[23] J. W. Barrett and R. P. Linstead, *J. Chem. Soc.* 611 (1963).



A B C

the solvolysis of Δ^5-cholestene-3β, 19-diol 3-*p*-toluenesulphonate (IX). Under hydrolytic conditions which favour kinetic control, aqueous acetone with sodium acetate buffer, Δ^5-cholestene-3β, 19-diol 3-*p*-toluenesulphonate (IX) yielded about 95% of 3α, 5-cyclocholestene 6β, 19-diol (XII).[14] Thin layer chromatographic analysis of the reaction product revealed the presence of about 1–2% of Δ^5-cholestene-3β, 19-diol (IV).[14] The product of intramolecular addition of the C_{19}-hydroxyl group to C_6, 3α, 5-cyclo-6β, 19-oxidocholestene (XIII)[14] was not formed. The stability of this oxide under the solvolytic conditions employed was established in a separate experiment. Similar hydrolysis of Δ^5-cholestene-3β-ol 19-al 3-*p*-toluenesulphonate (VIII) yielded predominantly 3α, 5-cyclocholestane-6β-ol-19-al (XIV) and a trace of Δ-cholestene-3β-ol-19-al (VII).



IX XII XIII

The probable reason for lack of formation of 3α, 5-cyclo-6β, 19-oxidocholestane (XIII) in the hydrolysis of Δ^5-cholestene-3β 19-diol 3-*p*-toluenesulphonate (IX) is the prohibitive amount of ring strain resulting from the AB *trans* fusion of the oxide ring. In the case of bicyclo [3.3.0.]-octane, the heat of combustion difference between the *cis* and *trans* forms is 6·0 kcal/mole.[23] Introduction of an oxygen atom into the 3-position does reduce this energy difference,[24] however, the *cis* is still the more stable.

It is somewhat surprising that the kinetically demonstrable interaction of the C_{19}-hydroxyl group in the transition state for ionization does not influence the product forming step. The stereoelectronically controlled axial attack of solvent at C_6 is not reversed. Were a stronger interaction present between these centres one

[24] L. N. Owen and A. G. Peto *J. Chem. Soc.* 2383 (1955).

would predict α-attack. This result indicates that the electronic influences are important in the rate determining ionization step but rather unimportant in the product forming step. One alternative explanation for the stereochemical course of this reaction, which cannot be excluded on the basis of the present data, is that solvent attacks at C_{19} with transfer of C_{19} oxygen to C_6.[25] This possibility is under investigation.

In conclusion, it is felt that these results, along with other similar studies,[5,6] point up the potentially important influence of distant groups upon reactive centres quite far removed. Qualitative observation of such rate variations are frequently encountered in steroidal reactions. The present study lends quantititive reality to such observations.

EXPERIMENTAL[27]

The rates of solvolysis of the tosylates were measured titrimetrically in anhydrous acetic acid according to the method of Winstein and Adams.[28] An amount of the sample, necessary to yield a solution approximately 1×10^{-2}M, was weighed in a 50 ml volumetric flask, and acetic acid was filled up to the mark. As soon as the solution was complete, about 5·5 ml portions were sealed in ampoules and immersed at one time in a constant temp bath. At appropriate times an ampoule was removed from the bath and the reaction terminated by quenching in a dry ice/acetone bath. The time of the first ampoule was taken as the "zero time". The ampoule was then brought to room temp, opened, and 5 ml pipetted out into an erlenmeyer flask for analysis. The amount of *p*-toluenesulphonic acid liberated was determined by titration with standardized sodium acetate in glacial acetic acid by use of a 5 ml microburette. The indicator used was bromphenol blue in the form of a saturated acetic acid solution (ca. 0·1%). The indicator is colourless in acidic acid solution, dim yellow in neutral solution, and brilliant yellow in basic solution.

Fluctuations in the temp of the baths used did not exceed 0·05° during a run. The thermometers were calibrated at the National Bureau of Standards.

Fisher reagent grade acetic acid was kept under reflux with chromic anhydride for 10 hr to remove oxidizable contaminants. Water was removed by treatment with triacetyl borate,[29] which was prepared by warming 1 part of boric acid with 5 parts (by wt.) of acetic anhydride to 60°. The fraction which distilled between 117–118° was collected and precautions were taken to minimize exposure to atmospheric moisture.

The sodium acetate reagent was prepared by dissolving reagent grade sodium carbonate in glacial acetic acid, and making the solution up to volume. It was made approximately 1×10^{-2}M and the strength determined by titration with perchloric acid in glacial acetic acid. A solution of 0·01N perchloric acid was prepared by placing 2·5 ml acetic anhydride in a 500 ml volumetric flask which was ice cooled and adding to it 0·5 ml 70–72% perchloric acid. The solution was made up to mark with glacial acetic acid, and standardized with weighed amounts of acid potassium phthalate, crystal violet being used as the indicator.

Rate constants were determined graphically by measuring the slope of plots of $\log_{10}(a - x_0)/(a - x)$ against time, and individual runs were followed for five half lives.

[25] We wish to thank Prof. P. vR. Schleyer, Princeton University, for suggesting this alternative possibility

[26] We wish to thank J. C. Orr, Syntex, for supplying us with an authentic sample.

[27] All m.ps were taken on a calibrated Fisher–Jones melting block apparatus and are uncorrected. Specific rotations were measured in $CHCl_3$ using a Rudolph Polarimeter (Model 80). IR spectra were taken on a Perkin–Elmer Infracord Spectrophotometer (Model 137). CCl_4 was used as solvent unless otherwise indicated. The microanalysis were performed by George I. Robertson Jr., 52 West End Avenue, Florham Park, New Jersey and by Chemco, Inc., 1790 Lanier Place, Northwest, Washington 9, D.C. NMR spectra were recorded at 60 MC/sec, on a Varian Model A-60 Spectrophotometer. CCl_4 was the solvent used unless otherwise specified. Thin layer chromatography was done using Silica Gel (E. Merk, Germany) and cyclohexane–ethyl acetate as the solvent mixture. Anhydrous $MgSO_4$ was used as the drying agent.

[28] S. Winstein and R. Adams, *J. Amer. Chem. Soc.* **70**, 838 (1948).

[29] L. F. Fieser, *Experiments in Organic Chemistry* (3rd. Edition) p. 281. D. C. Heath, Boston (1957).

5α-Bromo-6β, 19-oxidocholestane-3β-ol 3-acetate (III)

To 350 ml cyclohexane, lead tetraacetate (13·0 g; 0·0293 mole), previously dried over (P_2O_5), and 7·0 g dry $CaCO_3$ were added. This system was kept at reflux for 40 min by means of a 500 watt lamp. Then freshly resublimed I_2 (3·70 g; 0·0146 mole) and II (3·0 g; 0·0057 mole) were added and the reaction mixture was kept at reflux for an additional hr. The insoluble white residue was removed by filtration through Celite. The pink coloured filtrate first was washed with 200 ml 30% $Na_2S_2O_3$ (the pink colour is dispersed) and then with water. The solution was dried and concentrated *in vacuo* to dryness. Crystallization of the crude product from acetone yielded 2·9 g of III, m.p. 158–159°, $[\alpha]_D^{30°}$ −30° (*c*, 1·3), lit 154–155°[12b] and 149°.[13b]

IR absorption peaks observed at 6·65 and 11·7 μ are assigned to the 6β,19-oxide group.

Δ⁵-Cholestene-3β, 19-diol 3-acetate (IVa)

To a solution of III (3·0 g; 0·0057 mole) in 100 ml 95% EtOH, 20·0 g of activated Zn was added. After a period of 25 hr at reflux the hot solution was filtered through Celite. Half the EtOH was removed by distillation, and an approximately equal volume of water was added. The solution was then further concentrated to ½ volume. The product was isolated by extraction with ether and purified by crystallization from acetone. A yield of 2·02 g IVa was obtained, m.p. 120–121°, undepressed upon admixture with an authentic sample.[26]

Δ⁵-Cholestene-3β, 19-diol (IV)

(a) To a solution of IVa (750 mg; 0·0017 mole) in 50 ml EtOH, NaOH (1 g) was added and the resulting solution kept at reflux for 2 hr. Ice water was then added followed by concentration *in vacuo*. The resulting solution was thoroughly extracted with ether and the combined extracts washed with water. After drying, and concentration to dryness, the residue was crystallized from MeOH. After recrystallization from MeOH a yield of 600 mg material, m.p. 151–152° was obtained.

(b) A solution of XII[14] (100 mg) in 20 ml acetone containing 0·5 ml 1N H_2SO_4 diluted with 1 ml water was refluxed for 0·5 hr. The solution was neutralized with $NaHCO_3$aq, extracted with ether, dried, and the ether extracts concentrated to dryness. Crystallization of the crude product from EtOH yielded 90 mg IV[14] m.p. 156–157°.

Δ⁵-Cholestene-3β-ol-19-al 3-acetate (V)

To a solution of IVa (10 g; 0·22 mole) in 200 ml freshly distilled acetone, 9 ml of 8N chromic acid was added dropwise at 15°. Ten minutes after completion of the addition, the reaction mixture was poured into ice water and the aqueous suspension extracted with ether. Isolation of the product gave 9·5 g of acetoxy-aldehyde V, m.p. 103–104°. The analytical sample had m.p. 105–106, $[\alpha]_D^{28°}$ −198° (*c*, 1·02). (Found: C, 78·62; H, 10·06 $C_{29}H_{46}O_3$ requires: C, 78·68; H, 10·47%). NMR – 1·97 ppm ($OCOCH_3$), 4·5 ppm (C olefinic proton) and 9·59 ppm (CH = O).

Δ⁵-Cholestene-3β-ol-19-al (VII)

A solution consisting of V (1·0 g) and K_2CO_3 (1·0 g) in 50 ml MeOH was heated at reflux for 10 hr. Ice was then added and the resulting suspension concentrated *in vacuo* to ½ its original volume. The solution was extracted with ether, dried, and concentrated to dryness *in vacuo*. Crystallization from MeOH yielded 850 mg VII, m.p. 137–139°. Recrystallization from MeOH gave material, m.p. 141–143°, $[\alpha]_D^{27°}$ −193° (*c*, 1·1). (Found: C, 80·94; H, 11·05 $C_{27}H_{44}O_2$ requires: C, 80·95; H, 11·05%).

Δ⁵-Cholestene-3β-ol-19-al 3-p-toluenesulfonate (VIII)

p-Toluenesulphonyl chloride (4·0 g) was added to VII (4·0 g) in 7 ml dry pyridine and the resulting solution allowed to stand overnight at room temp. Addition of ice caused separation of the crystalline product which was washed with water and dried by warming at 0·001 mm press. overnight. Crystallization from ether gave 4·33 g VIII, m.p. 154–156°, recrystallized from ether, 155–156°, $[\alpha]_D^{29°}$ −167° (*c*, 1·0). (Found: C, 73·49, H, 8·99 $C_{34}H_{50}SO_4$ requires: C, 73·33; H, 9·41%).

Δ⁵-Cholestene-3β, 19-diol 3-p-toluenesulphonate-19-acetate (IXa)

Compound IX (970 mg) was dissolved in 8 ml dry pyridine and 1·5 ml acetic anhydride was added. After standing at room temp overnight, ice was added and the resulting suspension extracted with

ether. The ether extracts were washed in turn with water, dil. HClaq, sat. $NaHCO_3$aq and finally dried and concentrated *in vacuo*. Crystallization of the resulting product from pentane gave 860 mg, m.p. 85–86°, $[\alpha]_D^{28°}$ −39° (*c*, 1·4). (Found: C, 72·18; H, 9·23 $C_{36}H_{54}O_5S$ requires: C, 72·18, H, 9·10%).

Δ^5-Cholestene-3β, 19-diol 3-acetate-19-methyl ether (XIa)

To a stirred solution of IVa (250 mg; 0·56 mmoles) in 15 ml methylene chloride and 0·25 ml conc fluoroboric acid, 20 ml 0·276N diazomethane was added dropwise over a period of 15 min at 0°. After stirring for 15 min, an additional 0·1 ml fluoroboric acid along with 10·0 ml diazomethane was added over a period of 10 min. After completion of the addition, the reaction mixture was stirred for a further 20 min, Na_2CO_3aq added till a neutral reaction, then water was added and the product isolated by extraction with ether. The crude product was purified by recrystallization from acetone to yield 200 mg of XIa, m.p. 109–110°. (Found: C, 78·50; H, 10·75; $C_{30}H_{50}O_3$ requires: C, 78·55; H, 10·99%).

Δ^5-Cholestene-3β, 19-diol 3-methyl ether (XIb)

Δ^5-Cholestene-3β,19-diol 3-acetate, (1·2 g) was dissolved in 150 ml MeOH and 1 g K_2CO_3 in 15 ml water was added. After 3 hr at reflux, ice was added and the solution concentrated, extracted with ether and the ether extracts were dried and concentrated *in vacuo*. Crystallization of the crude product from acetone afforded 940 mg of XIb with m.p. 140–141°. (Found: C, 80·45; H, 11·60; $C_{28}H_{48}O_2$ requires: C, 80·71; H, 11·61%).

Δ^5-Cholestene-3β,19-diol 3-p-toluenesulphonate-19-methyl ether (XI)

Compound XIb (820 mg) was dissolved in 1 ml anhydrous pyridine and *p*-tolunesulphonyl chloride (820 mg) was added. After standing at room temp overnight, ice was added and the product isolated by extraction with ether. The ether extracts were washed with water, dried, and concentrated to dryness. Recrystallization of the crude product from acetone afforded 830 mg of XI, m.p. 126·5–127·5 with dec. (Found: C, 73·70; H, 9·52; $C_{35}H_{54}SO_4$ requires: C, 73·64; H, 9·54%).

Δ^5-Cholestene-3β-ol-19-al 3-p-toluenesulphonate-19-thioacetal (X)

This compound was prepared and crystallized from low boiling pet. ether. The m.p. of X is 122–124° with dec. (Found: C, 68·66; H, 8·57; $C_{36}H_{54}S_2O_3$ requires: C, 68·53; H, 8·63%).

Solvolysis of Δ^5-cholestene-3β,19-diol 3-p-toluenesulphonate (IX)

Ester IX (425 mg; 0·75 mole), was dissolved in 50 ml acetone and a solution of 425 mg sodium acetate in 10 ml water was added. The resulting solution was heated under reflux for 16 hr. At the end of this time ice was added followed by concentration *in vacuo*. The precipitated crystalline product (XII) was filtered and recrystallized from acetone to yield 300 mg (97·6% yield), m.p. 137–138·5°, $[\alpha]_D^{28°}$ +47 (*c*, 1·2). The IR spectrum of XII showed strong absorption at 3·0 μ (OH). The NMR spectrum of XII possessed bands at δ = 0·25 and 0·55 ppm (cyclopropyl protons at C_3 and C_4) δ = 3·17, 3·23, 3·26 (C_6 equatorial proton Jae = Jee = 3·00 c/s) and δ = 3·58, 3·75, Jab = 10 c/s (C_{19} methylene proton). Thin layer chromatographic analysis using ethyl acetate–cyclohexane (1:1) gave R_f values of 0·70 for XII and 0·25 for IV. This latter material was shown to be present in trace amounts in the above hydrolysis. Furthermore, no XIII was found to be present by TLC analysis.

Buffered solvolysis of Δ^5-cholestane-3β-ol-19-al 3-p-toluenesulphonate (VIII)

To a solution of VIII (350 mg; 0·63 mole) in 25 ml acetone, potassium acetate (400 mg) in 5 ml water was added and the solution heated under reflux. After 40 hr the reaction was halted by dilution with ice water. The organic solvent was removed under vacuum and the resulting precipitate separated washed with water, and dried. It was crystallized from acetone to yield 70 mg, m.p. 100–104, $\lambda_{max}^{CCl_4}$ 2·7 (w), 2·8, 3·6 and 5·8 μ among other bands. The NMR showed absorption at δ = 0·50 and 0·83 (cyclopropyl protons at C_3 and C_4) broad unresolved peak at δ = 3·0. (C_6-*a*-proton) and a sharp singlet at δ = 9·9 (aldehydic proton). Thin layer chromatographic analysis of the crude hydrolysis product in cyclohexane–ethyl acetate (5:1) revealed products with R_f 0·9, 0·7, 0·63, 0·42. The last value, 0·42, corresponds to 3α,5-cyclocholestane-6β-ol-19-al and 0·25 corresponds to VII.

Δ^5-Cholestene-3β,ol-19-al 3-acetate-19-thioacetal (Xb)

To a solution of V (500 mg) in 5 ml glacial acetic acid, 1·0 ml ethane dithiol and 2·5 ml boron trifluoride etherate was added. After 15 min at room temp, the precipitated product was separated by filtration. It was washed with water and crystallized from acetone to yield 500 mg, m.p. 159–161°, $[\alpha]_D^{29°}$ −81° (*c*, 1·06). Found: C, 71·85; H, 9·73; $C_{31}H_{50}O_2S_2$ requires: C, 71·74; H, 9·71%).

Δ^5-Cholestene-3β-ol-19-al-19-thioacetal (Xa)

A solution containing acetate Xb (300 mg) and K_2CO_3 (300 mg) in 50 ml MeOH was heated under reflux for 2 hr. Addition of ice water caused a gelatinous semi-crystalline solid to separate which was collected and dried. Recrystallization from acetone yielded 230 mg of Xa, m.p. 148–149°, $[\alpha]_D^{27°}$ −88° (*c*, 1·1). (Found: C, 72·70; H, 10·00; $C_{29}H_{48}OS_2$ requires: C, 73·07; H, 10·15%).

Δ^5-Cholestene 3β,19-methylal (VI)

To a solution of V (2·0 g) in 100 ml MeOH, K_2CO_3 (1·0 g) in 5 ml water was added and the resulting solution heated under reflux for 1 hr. After adding ice and neutralizing with dil. H_2SO_4, MeOH was removed *in vacuo*. The product was isolated by extraction with ether. The ether extracts were dried, concentrated to dryness and crystallized from acetone–MeOH to yield 1·8 g, m.p. 166–168, $[\alpha]_D^{26°}$ −66° (*c*, 1·2), $\lambda_{max}^{CCl_4}$ 3·3; 6·8; 7·22; 8·29; 8·42; 8·98; 9·08; 9·71; 9·94; 10·72 μ. The NMR spectrum displayed bands at δ = 0·72 ppm (C-18 methyl); δ = 3·36 (—O—CH_3) and δ = 4·64 ppm (—$\underset{|}{\overset{|}{C}}$—$OCH_3$). (Found: C, 81·38; H, 11·05; $C_{28}H_{46}O_2$ requires: C, 81·12; H, 11·19%).

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