# The Solvolysis of 4α- and 4β-Methylcholesteryl p-Toluenesulfonates. A Kinetic Study. II[1,2]

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The first-order rate constants for acetolysis of 4α-methylcholestanyl, 4β-methylcholestanyl, 4α-methylcholesteryl, and 4β-methylcholesteryl, p-toluenesulfonate esters have been determined at various temperatures. The rates relative to cholestanyl p-toluenesulfonate at 50° are, for 4α-methylcholestanyl, 1.3; for 4β-methylcholestanyl, 2.4; for 4β-methylcholesteryl, 475; and, for 4β-methylcholesteryl, 2300. These relative rate variations are discussed in terms of the conformational strain effects upon the ground state and the transition state resulting from the introduction of an axial or equatorial methyl group at the C-4 position of the cholesteryl molecule. Specifically, a distortion of the A ring is considered to result in the 4β-methyl (axial) case. This distortion, either a flattening of the ring or conversion to a skewboat, interferes with the geometric conditions required for effective homoallylic participation. In the 4α-methylcholesteryl case, no corresponding conformational change of the A ring occurs and the rate enhancement (20-fold) over cholesteryl p-toluenesulfonate is rationalized in terms of a "symmetrical" nonclassical ion in which the σ-electrons of the C-4–C-5 bond are delocalized. The hitherto undetected *i*-steroid, 3α,5-cyclo-4β-methylcholestan-6β-ol, has now been isolated in 2–5% yield from the buffered hydrolysis of 4β-methylcholesteryl p-toluenesulfonate. Evidence is presented for the artifactitious origin of the 80% of 4-methyl-$\Delta^{3,5}$-cholestadiene in the solvolysis of 4β-methylcholesteryl p-toluenesulfonate. The large amount of steric strain present in the *i*-steroid accounts for its extremely facile dehydration to diene.

It is well recognized that various carbocyclic rings in polycyclic compounds such as steroids and triterpenes may undergo conformational changes in order to relieve steric interactions between nonbonded groups. Often this type of change among six-membered systems involves a distortion from a chair to either a flattened chair[4] or a boat-like conformation.[5] This phenomenon has been investigated widely with the aid of dipole moment measurements,[4,6] optical rotatory dispersion,[7a,b] n.m.r.,[8] and ultraviolet absorption,[8] and also has been implicated from the nature of products formed in various reactions.[9a,b]

Study of the relative rates of solvolysis of steroidal compounds which might show a sensitivity to conformational changes in the ring structure appeared to offer a means of correlating deviation from a chair form with solvolytic behavior. The homallylic 3β-tosyloxy-$\Delta^5$ system present in the cholesteryl series is suitable for this purpose since the observed rate of solvolysis may be assumed to be dependent upon the C-3–C-5 distance and the orientation of the incipient vacant p-orbital at C-3 with respect to the C-5–C-6 double bond.[10a,b] This is a consequence of the geometric requirements for homoallylic participation and the quantum mechanical conditions for optimal overlap.[10a,b] Thus, if introduction of an alkyl group into the A ring of cholesteryl p-toluenesulfonate caused a substantial distortion of the A or B ring from a chair form, and this were retained in the transition state, a proportional change in the rate of solvolysis should be observed. The relative rates of structurally related compounds depend primarily upon differences between the ground state and transition state energies. In endothermic processes, such as solvolytic reactions, the transition state is normally thought to resemble the product, and in the solvolysis of cholesteryl p-toluenesulfonate the product is the homoallylic intermediate after the rate-limiting activation step. 4α- and 4β-methylcholesteryl p-toluenesulfonates were selected as model compounds for the study of the effect of alkyl groups in the A ring upon the rate of solvolysis.

## Results and Discussion

The synthesis[2,11a] and products of solvolysis of 4α- and 4β-methylcholesteryl p-toluenesulfonate[2,11b] have already been reported. The corresponding saturated alcohols are known[12a,b] and the p-toluenesulfonate esters have been prepared in the present investigation. Rates of acetolysis were determined titrimetrically at various temperatures and the pertinent kinetic and thermodynamic data are collected in Table I.

The most striking feature of the rate data presented in Table I is the relatively large enhancement in rate of acetolysis caused by substitution of a methyl group at C-4. Furthermore, the configuration of the methyl is determinative. The relative rate of the equatorial C-4 methyl compound is 20 times faster than cholesteryl p-toluenesulfonate while the axial methyl derivative is only 3.8 times faster. In the saturated series the effects are smaller and in the reverse direction. The C-4 equatorial methyl derivative, 4α-methylcholestanyl p-toluenesulfonate, solvolyzes only 1.3 times faster than cholestanyl p-toluenesulfonate, and the C-4 axial methyl compound is 2.4 times faster. Comparison of the rates for the saturated and unsaturated derivatives among themselves is also instructive; the ratio for the 4α-methyl compounds is 1800, while that for the

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for support of this project under Grant 1347-A4; (b) taken in part from the Doctoral Dissertation of R. M. de Sousa, The Catholic University of America, 1964.

(2) For part I, which deals with the products of solvolysis of the title compounds, see ref. 3.

(3) R. M. Moriarty and R. M. de Sousa, *J. Org. Chem.*, **28**, 3072 (1963).

(4) N. L. Allinger and M. A. Da Rooge, *J. Am. Chem. Soc.*, **84**, 4561 (1962).

(5) For a recent review of nonchair conformations, see M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962).

(6) H. R. Nace and R. B. Turner, *J. Am. Chem. Soc.*, **75**, 4063 (1953).

(7) (a) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *ibid.*, **80**, 4001 (1958); (b) J. S. E. Holker and W. B. Whalley, *Proc. Chem. Soc.*, 464 (1961).

(8) M. Gorodetsky and Y. Mazur, *Tetrahedron Letters*, **No. 4**, 227 (1964).

(9) (a) D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957); (b) J. Levisalles, *Bull. soc. chim. France*, 551 (1960).

(10) (a) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954); (b) C. W. Shoppee and D. F. Williams, *J. Chem. Soc.*, 2488 (1956).

(11) (a) S. Julia, J. P. Lavaux, S. R. Pathak, and G. H. Whitham, *Compt. rend.*, **251**, 733 (1960); (b) S. Julia, J. P. Lavaux, S. R. Pathak, and G. H. Whitham, *ibid.*, **256**, 1537 (1963).

(12) (a) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958); (b) S. Julia and J. P. Lavaux, *Bull. soc. chim. France*, 1223 (1963).

TABLE I

FIRST-ORDER RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE ACETOLYSIS OF 4-METHYLCHOLESTERYL *p*-TOLUENESULFONATE ESTERS

| *p*-Toluenesulfonate esters | Temp., °C. | $10^4$ *k*, sec.$^{-1}$ | Relative rate | $\Delta H$, kcal./mole | $\Delta S^*$, e.u. |
|---|---|---|---|---|---|
| 3-*p*-Toluenesulfonate cholestanyl | 50 | 0.011 | 1 | | |
| 4$\alpha$-Methylcholestanyl | 50 | 0.014 | 1.3 | | |
| 4$\beta$-Methylcholestanyl | 50 | 0.026 | 2.4 | | |
| 4,4-Dimethylcholestanyl[a] | 50 | 0.08 | 7.4 | | |
| Cholesteryl | 50 | 1.27 | 117 | 24.4 | −1.0 |
| 4$\alpha$-Methylcholesteryl | 50 | 25.8 | 2300 | 21.6 | −4.0 |
| | 43 | 11.9 | | | |
| | 35 | 5.3 | | | |
| 4$\beta$-Methylcholesteryl | 50 | 5.15 | 475 | 22.3 | −5.1 |
| | 43 | 2.15 | | | |
| | 35 | 0.95 | | | |
| 4,4-Dimethylcholesteryl | 50 | 15.8 | 1460 | | |

| Rate ratio at 50° | 4H | 4$\alpha$-$CH_3$ | 4$\beta$-$CH_3$ | 4,4-di$CH_3$ |
|---|---|---|---|---|
| *k* cholesteryl series/*k* cholestanyl series | 117 | 1800 | 200 | 200 |

[a] C. W. Shoppee and G. A. R. Johnston, J. Chem. Soc., 3261 (1961).

4$\beta$-methyl derivatives is 200. The relative rates for the reference pair, cholestanyl–cholesteryl, is 117.

These results pose two questions of fundamental interest in connection with homoallylic systems: (a) what factors account for the rate enhancement resulting from alkylation at the C-4 position, and (b) why is the magnitude of the rate acceleration dependent upon the axial or equatorial orientation of the methyl group?

An answer to the first question lies in the nature of the intermediary homoallylic ion formed in these solvolytic reactions. Winstein and Kosower[13] mentioned the possibility of the existence of a "symmetrical contributor" (A) to the homoallylic cation involved in both the solvolysis of cholesteryl *p*-toluenesulfonate and 3$\alpha$,5-cyclocholestan-6$\beta$-ol trichloroacetate.

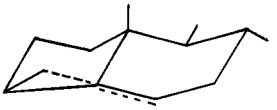
$^+$A

symmetrical



$^+$B

unsymmetrical



$^+$C

unsymmetrical

Further evidence for this formulation of the cholesteryl cation was provided recently by Whitham and Wickramasingle[14] in their study of the solvolysis of 3$\beta$-hydroxymethyl-$\Delta^5$-A-norcholestene *p*-toluenesulfonate. In the case of the cholesteryl cation, the symmetrical form of the ion A must be considered to make only a minor contribution owing to the relative inefficiency of the primary center at C-4 to stabilize a substantial amount of positive charge. However, introduction of a methyl group at this position now changes the picture owing to the well-recognized stabilization of positive centers by increased alkylation at the positive carbon.[15] The rate enhancement, therefore, is explicable in terms of the increased delocalization of charge in the transition state resulting from the heightened contribution of the symmetrical ion A.

Now we turn to the question of the relatively smaller rate enhancement observed for 4$\beta$-methylcholesteryl *p*-toluenesulfonate and a corollary question, namely, why the presence of two methyl groups at C-4 does not lead to an even greater effect than that observed for the C-4 equatorial monomethyl derivative. The slower rate of 4$\beta$-methylcholesteryl *p*-toluenesulfonate relative to the 4$\alpha$-methyl compound must be due to a steric effect since there is little reason to believe that the nature of the electronic effect of the methyl substituent would vary with its orientation. We propose that the slower rate of solvolysis of the 4$\beta$-methylcholesteryl *p*-toluenesulfonate is due to a distortion of the A ring. The distortion is likely to take the form of a flattening of the A ring in order to relieve the C-4–C-10 1,3-diaxial interaction of the two methyl groups.[4] The result of such flattening is an increase in the C-3–C-5 distance. Since $2p\pi$–$\sigma$ overlap in the homoallylic ion falls off rapidly with increasing 1,3-internuclear distance,[10a,b] the resulting poorer overlap in the flattened A ring structure leads to a less stable homoallylic ion.[16] The lessened anchimeric assistance provided by the C-5–C-6 double bond is reflected in a higher activation energy for solvolysis. Figure 1 depicts these relationships in the form of an energy profile. This illustrative representation is not meant to imply more than *relative* energy differences. Differently stated the presence of the 1,3-dimethyl interaction in the first transition state for ionization and also in corresponding intermediary homoallylic ion destabilizes the ion and raises the activation energy for its formation.

In order to gain information about the conformation of 4$\beta$-methylcholesteryl *p*-toluenesulfonate, the n.m.r. spectra of 4$\alpha$- and 4$\beta$-methylcholesteryl acetates were compared. It is known that specific functional groups in the vicinity of the C-19 methyl group exert self-consistent chemical shift changes.[18] These displace-

(13) S. Winstein and E. M. Kosower, *J. Am. Chem. Soc.*, **81**, 4399 (1959).

(14) G. H. Whitham and J. A. F. Wickramasingle, *J. Chem. Soc.*, 1655 (1964).

(15) A 75-fold rate increase in hydrolysis has been observed by R. Sneen [*J. Am. Chem. Soc.*, **80**, 3982 (1958)] for the substitution of a methyl group for hydrogen at C-6 in cholesteryl *p*-toluenesulfonate.

(16) A somewhat arbitrary analysis of the rate data may be made within the frame work of a chair–boat equilibrium. The first assumption to be made in this treatment is that the boat form A ring of 4$\beta$-methylcholesteryl *p*-toluenesulfonate does not allow homoallylic participation. Inspection of models reveals that this is not an unreasonable assumption. In order to estimate the rate of solvolysis of a boat form we must take into account the fact that the 3$\beta$-tosyloxy group is axial and *trans* coplanar with the 4-H, a situation similar to that of epicholesteryl toluenesulfonate. Since the relative rate of acetolysis of epicholesteryl *p*-toluenesulfonate to that of cholestanyl *p*-toluenesulfonate is 15:1, the rate of acetolysis for the boat-form of 4$\beta$-methylcholesteryl-*p*-toluenesulfonate may be estimated to be *ca.* 15($k$4$\beta$-methylcholestanyl tosylate) = $0.39 \times 10^{-4}$ sec.$^{-1}$. Second, we assume that the rate of solvolysis of the chair form of 4$\beta$-methylcholesteryl *p*-toluenesulfonate is close to the 4$\alpha$ analog. Following the method presented by Eliel[17] we allow [C] = concentration of the chair, and [B] = concentration of the boat, then $K$ = [B]/[C] and the observed rate = $k_c$[C] + $k_b$[B] = $k$([C] + [B]), where $k_c$ = rate constant for solvolysis of the chair form, $k_b$ = rate constant for solvolysis of the boat form, and $k$ = observed rate = 5.15. This calculation leads to the interesting conclusion that in the

$$5.15 = k = \frac{k_bK + k_c}{K + 1} = \frac{K(0.39) + 25.8}{K + 1} \text{ or}$$

$$K = 4.4 = \frac{[B]}{[C]}, \therefore [B] \backsim 80\%, [C] \backsim 20\%$$

ground state 4$\beta$-methylcholesteryl *p*-toluenesulfonate exists to the extent of about 80% in the boat form.

(17) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 235.

(18) R. F. Zurcher, *Helv. Chim. Acta*, **44**, 1380 (1961).

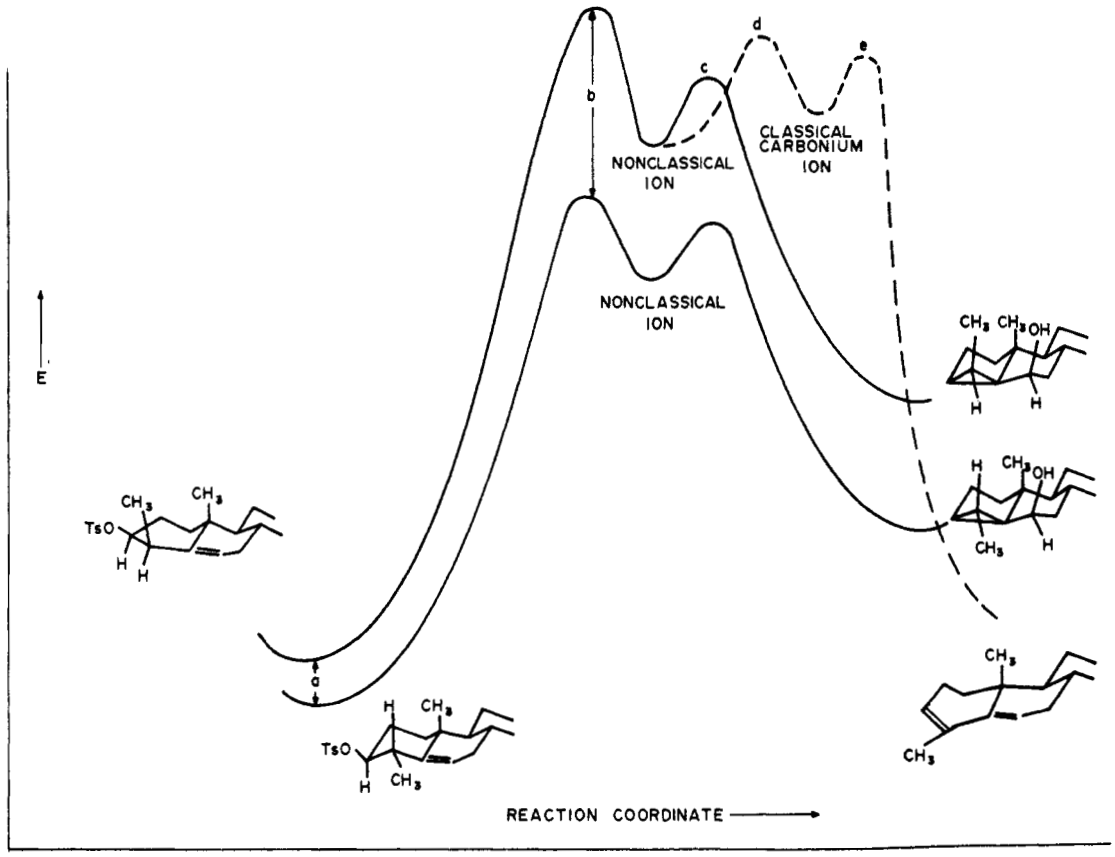
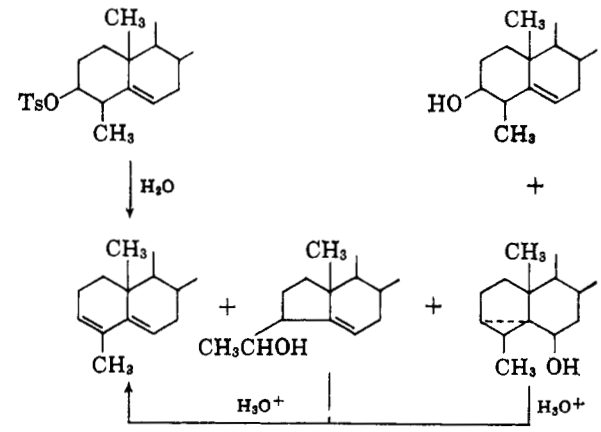



Figure 1.—Energy Profile for formation of the 4α- and 4β-methylcholesteryl ions: a, ground state difference in energy between 4α- and 4β-methylcholesteryl p-toluenesulfonates; b, difference in transition state energy for their solvolyses; c, energy barrier for i-steroid formation; d, energy barrier for rearrangement of nonclassical ion to classical carbonium ion precursor of diene; e, energy barrier for diene formation.

ments are additive and depend upon the orientation of the functional group with respect to the angular methyl group. The C-19 methyl peak of 5α-androstane appears at τ 9.225 and long-range deshielding effects resulting from the introduction of a C-5–C-6 double bond and 3β-acetoxy group shift the C-19 resonance by τ 0.233 and 0.050, respectively. In agreement with prediction, the C-19 methyl peaks of 4α-methylcholesteryl and cholesteryl acetates appear at τ 8.98. In the 4β-methyl and 4,4-dimethylcholesteryl acetates, however, the C-19 methyl resonance was shifted downfield to τ 8.94 and 8.93 respectively. This corresponds to extra deshielding which would be the case for a distorted A ring or a boat form A ring.

The predominant product (80%) isolated from the solvolysis of 4β-methylcholesteryl p-toluenesulfonate is 4-methyl-$\Delta^{3,5}$-cholestadiene.[3,11] This result contrasts with the very small amount of diene which is formed in the solvolyses of cholesteryl p-toluenesulfonate and 4α-methylcholesteryl p-toluenesulfonate. The possibility that the diene derives from a boat form of the A ring of 4β-methylcholesteryl p-toluenesulfonate has been discussed by both the present authors[3] and more recently by Julia, Lavaux, Pathak, and Whitham.[19]

The reason for advancing this hypothesis is that a *trans* diaxial relationship exists between the C-3 tosyloxy group and the C-4 proton in the boat form A ring; *i.e.*, the requisite stereoelectronic requirement for elimination is present. It has been found, however,




that the diene is not the product of a primary process but arises at least in part *via* dehydration of an alcohol precursor. Four experimental facts support this claim: (a) contrary to previous claims of the lack of formation of a cyclosterol in the solvolysis of 4β-methylcholesteryl p-toluenesulfonate,[3,11] we have now succeeded in isolating in about 2% yield 3α,5-cyclo-4β-methylcholestan-6β-ol; (b) the instability of this compound is evidenced by the fact that, upon standing in deuteriochloroform for 1 week, it underwent partial dehydration to the diene (this change was observed by n.m.r. and by thin layer chromatography); (c) the concentration of diene in the crude reaction product immediately after hydrolysis was found to be of the order of 40–50%, assayed by quantitative ultraviolet measurement, and this percentage rose to 80% after it had been allowed

(19) S. Julia, J. P. Lavaux, S. R. Pathak, and G. H. Whitham, *J. Chem. Soc.*, 2633 (1964). The authors wish to acknowledge a preprint of this paper supplied by Dr. Witham.

to remain upon a column of alumina for 4 hr.; and (d) attempted acid-catalyzed rearrangement of 3α,5-cyclo-4β-methylcholestan-6β-ol yielded 4-methyl-$\Delta^{3,5}$-cholestadiene instead of 4β-methylcholesterol, the normal product of acid-catalyzed rearrangement of an *i*-steroid.

The previously undetected *i*-steroid had the correct elemental composition. Also the optical rotation, $[\alpha]^{27}D$ + 20, was indicative of an *i*-steroid (the change from a negative sign of rotation for the cholesteryl → *i*-cholestanyl transformation is diagnostic); absence of absorption in the olefinic region of the n.m.r. spectrum also agreed with expectation. Chromium trioxide–pyridine oxidation converted the *i*-sterol into the corresponding *i*-ketone, 3α,5-cyclo-4β-methylcholestan-6-one, which had absorption in the infrared at 5.92 μ (cyclopropyl ketone).

The above results suggest that a boat form conformation need not be invoked to explain the formation of 80% of 4-methyl-$\Delta^{3,5}$-cholestadiene in the buffered hydrolysis of 4β-methylcholesteryl *p*-toluenesulfonate. The large amount of diene isolated in the solvolysis probably comes from the *i*-steroid which is a very unstable compound and is prone to dehydrate readily. The instability results from the 1,3-diaxial relationship of the C-4 methyl, C-10 methyl, and C-6 hydroxyl groups. The *i*-steroid is the product of kinetic control. The diene may come from the same intermediate as the *i*-sterol, but it is the product of thermodynamic control. The strong driving force for formation of diene stems from the relief of nonbonded interactions in this compound. Figure 1 presents these relationships in terms of relative stability of ground states, transition states, intermediates, and products. A small energy barrier is considered to separate the nonclassical ion and the less stable classical one. Rearrangement of the intermediary ions may occur as well as dehydration of the *i*-sterol and formation of diene from a classical carbonium ion precursor.

## Experimental[20]

**Kinetic Procedure.**—The rates of acetolysis of the *p*-toluenesulfonate esters were measured titrimetrically by the method of Winstein and Adams.[21] An amount of sample necessary to yield a solution of approximately $1 \times 10^{-2}$ *M* was weighed into a 50-ml. volumetric flask and filled with acetic acid at room temperature. As soon as it dissolved, about 5.5-ml. portions were sealed in ampoules and placed into a constant temperature bath. At timed intervals, an ampoule was removed from the bath and frozen in a Dry Ice–acetone bath. (The first ampoule removed was taken to be at "zero time".) It was then allowed to come to room temperature and 5 ml. of the solution was pipeted out and titrated against standardized sodium acetate in glacial acetic acid. A saturated solution of bromophenol blue in acetic acid was used as an indicator.

Fisher reagent grade acetic acid was kept under reflux with chromic anhydride for 10 hr. It was then treated with triacetyl borate and distilled. The fraction of b.p. 117–118° was collected with precautions taken to minimize exposure to atmospheric moisture.

Sodium acetate solution of approximately $1 \times 10^{-2}$ *M* was prepared by dissolving reagent grade anhydrous sodium carbonate in the purified glacial acetic acid. Its strength was determined by titration with a standardized solution of perchloric acid in glacial acetic acid.

Fluctuations in the temperature of the baths used did not exceed 0.05° during a run. The thermometers were calibrated at the National Bureau of Standards, Washington, D. C. Rate constants were determined graphically by measuring the slope of plots of $\log (a - x_0)/(a - x)$ *vs.* time. The rates were studied up to about 5 half-lives. Thermodynamic quantities were calculated by means of the equation

$$k = \frac{kT}{h}\exp\left(\frac{\Delta S^*}{R}\right)\exp\left(\frac{-\Delta H^*}{RT}\right)$$

where $k$ is the reaction rate constant, $T$ is the absolute temperature, $\Delta H^*$ is the enthalpy of activation, and $\Delta S^*$ is the entropy of activation.

**4β-Methylcholestanyl *p*-Toluenesulfonate.**—A solution of 1 g. of 4β-methylcholesteryl acetate[11a] in 60 ml. of glacial acetic acid containing 1 drop of perchloric acid and 200 mg. of Adams catalyst was shaken in 1 atm. of hydrogen overnight under a pressure of 20 lb./in.$^2$ and at a temperature of 80°. The catalyst was filtered off and about 5 ml. of 20% sodium hydroxide solution was added. The solution was concentrated to a small volume and the steroid was precipitated by addition of water. It was filtered and then dissolved in ether, dried, and concentrated to dryness under reduced pressure. Crystallization from acetone yielded 0.6 g., m.p. 144–146° (lit.[12b] m.p. 145–146°). The acetate was saponified with potassium carbonate in aqueous methanol, and a yield of 0.5 g. of 4β-methylcholestan-3β-ol, m.p. 156–157°, was obtained after crystallization from methanol.

*Anal.* Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.51. Found: C, 83.48; H, 12.46.

The *p*-toluenesulfonate ester was prepared by allowing a solution containing 0.45 g. of 4β-methylcholestan-3β-ol and 0.45 g. of *p*-toluenesulfonyl chloride in 3 ml. of dry pyridine to stand for 3 days at room temperature. The ester was caused to precipitate by addition of ice. The precipitate was collected, washed, dissolved in ether, and dried, and then concentrated to dryness *in vacuo*. Crystallization from ether–pentane yielded 0.40 g. of 4β-methylcholestanyl *p*-toluenesulfonate, m.p. 102–103°.

*Anal.* Calcd. for $C_{35}H_{56}O_3S$: C, 75.50; H, 10.14. Found: C, 75.68; H, 9.84.

**Hydrolysis of 4β-Methylcholesteryl *p*-Toluenesulfonate.**—A solution of 2.0 g. 4β-methylcholesteryl *p*-toluenesulfonate in 200 ml. of acetone containing 20 ml. of water and 2.0 g. of potassium acetate was kept at reflux for 4 hr. The acetone was removed under vacuum and the product was isolated by extraction with ether. It was washed, dried, and evaporated to dryness. Care was taken to keep the temperature low during the work-up. An infrared spectrum on the crude product indicated that the hydrolysis of the *p*-toluenesulfonate ester was complete. The product was chromatographed on a column of 25 g. of neutral aluminum oxide. Elution with hexane yielded 0.75 g. of 4-methyl-$\Delta^{3,5}$-cholestadiene. Elution with benzene gave 0.16 g. of 3β-(1β-hydroxyethyl)-$\Delta^5$-A-norcholestene in the first two fractions, and 0.09 g. of 3α,5-cyclo-4β-methylcholestan-6β-ol, m.p. 73–74°, $[\alpha]^{27}D$ +20, in the next two fractions. This material was saturated (negative tetranitromethane test) and its n.m.r. spectrum had absorption in the τ 9.5–9.2 region but no absorption at 4.3.

*Anal.* Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 84.20; H, 12.22.

Chromium trioxide–pyridine oxidation of 3α,5-cyclo-4β-methylcholestan-6β-ol yielded a gum which had infrared absorption at 5.92 μ. (Further elution with benzene gave 0.01 g. of 4β-methylcholesterol.)

The crude product from hydrolysis of the ester as well as the purified samples obtained from chromatography were subjected to thin layer chromatography (t.l.c.) on silica gel with benzene–chloroform (1:1). The $R_f$ values obtained were, for 4-methyl-$\Delta^{3,5}$-cholestadiene, 0.96; 3α,5-cyclo-4β-methylcholestan-6β-ol, 0.61; 3β-(1β-hydroxyethyl)-$\Delta^5$-A-norcholestene, 0.52; and 4β-methylcholesterol, 0.30.

The purified sample of 3α,5-cyclo-4β-methylcholestan-6β-ol gave one spot, $R_f$ 0.61. The n.m.r. spectrum was determined and the sample allowed to stand in deuteriochloroform for 1 week. After this time t.l.c. on the product indicated two spots, $R_f$ 0.96 and 0.61. Also, the appearance of a vinyl proton could

(20) Melting points are uncorrected and were determined on a Fisher-Jones melting point block. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectra were determined on a Bausch and Lomb Model 505 recording spectrophotometer. N.m.r. spectra were determined on a Varian A-60 spectrophotometer operating at 60.0 Mc./sec. Optical rotations were taken in chloroform solution. Anhydrous magnesium sulfate was used as drying agent. Microanalysis were carried out by George I. Robertson, Florham Park, N. J.

(21) S. Winstein and R. Adams, *J. Am. Chem. Soc.*, **70**, 838 (1948).

be distinguished in the n.m.r. spectrum at $\tau$ 4.3, and the product gave a positive tetranitromethane test.

A solution of 10 mg. of 3$\alpha$,5-cyclo-4$\beta$-methylcholestan-6$\beta$-ol in 10 ml. of dioxane containing 1 ml. of 1 *N* sulfuric acid was allowed to stand at room temperature overnight. T.l.c. on the product after work-up indicated that dehydration to 4-methyl-$\Delta^{3,5}$-cholestadiene had taken place. No alcohol was detected.

4$\beta$-Methylcholesteryl *p*-toluenesulfonate (50 mg.) in 50 ml. of acetone containing 5 ml. of water and 50 mg. of potassium acetate was kept at reflux for 4 hr. It was worked up in the usual way with the temperature kept as low as possible. The crude product (32 mg.) was dissolved in 50 ml. of ethanol. A quantitative determination of ultraviolet absorption at 239 m$\mu$ indicated the presence of 47% 4-methyl-$\Delta^{3,5}$-cholestadiene. The solution was allowed to stand at room temperature for 1 week after which the ultraviolet absorption indicated 78% of the diene. The hydrolysis was repeated with 50-mg. samples of 4$\beta$-methylcholesteryl *p*-toluenesulfonate several times and the result was consistent within ±5%. The same result was obtained when the product was allowed to stand on a column of alumina for 6 hr. The percentage of diene (40–50% directly after hydrolysis) rose to 80–85% after elution from the column.

# Reduction of Esters of the Windaus Keto Acid by Sodium Borohydride

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The reactions of the keto esters IIb and IIc and the lactone III in 2-propanol with sodium borohydride have been studied intensively. The alkoxyborohydrides formed during the reductions react with 2-propanol yielding hydrogen. A boron-containing material has been isolated. These results, which are due to side reactions, and the mechanism of reduction of ester groups by borohydride are discussed.

Some years ago Schenker[3] suggested that the reduction of esters and lactones by sodium borohydride requires the presence of other groups such as hydroxyl. This view is in accord with a recent result[4] that a fully esterified sugar lactone gave only very poor yields of hemiacetal on treatment with borohydride.[5] In 1961, Atwater[7] obtained complex mixtures of lactones, hemiacetals, and in some cases diols from the borohydride reduction of $\delta$-keto esters derived from the cleavage of ring A or ring B of steroids. He concluded that the formation of the lactones was a prerequisite for further reduction (*cf.* ref. 8). In previous work,[9] we reduced a $\gamma$-keto ester with sodium borohydride to a mixture which included two epimeric diols. As the formation of a lactone intermediate *en route* to the predominant diol was unlikely for steric reasons, we proposed that for this compound, at least, the reduction of the ester group might proceed by way of an intramolecular transfer of a hydride ion (I, see Chart I). This mechanism involves an intramolecular reduction with an alkoxyborohydride, which should be a more powerful reducing agent than borohydride itself.[10] The results obtained by Barnet and Kent[11] support our suggestion. They found that under comparable conditions the yield of diol from borohydride reduction increases as one goes from $\gamma$- to $\beta$- to $\alpha$-keto esters; an intramolecular transfer of hydride (*cf.* I) would involve five- and six-membered rings with the $\alpha$- and $\beta$-keto compounds, respectively.

While working on another problem,[12] we observed that reduction of the keto ester IIb[13] with sodium borohydride gave a mixture of products including the lactone III,[13,14] the acetal IVb,[15] and the diol V.[14] These products were obtained as mixtures of stereoisomers at the 5-position. There appeared to be two possible paths for the reductions: II → VI → III → IVa → VII → V and II → VI → IX (*via* VIII) → VII → V. We decided to study the reaction by measuring the rate of disappearance of ketone in the reduction of IIb and IIc and by determining the rate of hydride consumption and carrying out product studies on the reductions of IIb, IIc, and III. From these studies we hoped to deduce whether III was an intermediate in the formation of IVb and V. The reactions proved to be more complicated than we had expected, and we could not attain our original objectives. However, the complications are of some intrinsic interest and so we report our results here.

## Results

The reductions of the methyl ester IIb, the isopropyl ester IIc, and the lactone III were carried out in solutions of 2-propanol; 2-propanol, unlike ethanol or methanol, does not react with sodium borohydride.[16,17] The courses of the reductions were followed by observing the disappearance of ketone (from the changes in the ultraviolet maxima at 290 m$\mu$) and the consumption of hydride (by titration). The reductions of the keto esters were carried out using 1 mole and 0.25 mole equiv. of sodium borohydride. The reduction of the lactone, which could be followed by titration only, was studied using 1 mole equiv. of borohydride.

(1) American Chemical Society Petroleum Research Fund Fellow, 1960–1963.

(2) The initial phases of this work were carried out at the Department of Chemistry at the University of South Carolina.

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(5) Brown and Rapoport[6] have observed that esters are reduced to primary alcohols using a large excess of sodium borohydride in methanol. However, under these conditions the effective reducing agent is probably trimethoxyborohydride rather than borohydride itself.

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