nitrile or acetonitrile–ether, decomposed at temperatures above 300°, but did not melt below 400°.

Anal. Calcd. for $C_{20}H_{15}N_2O_5Cl$: C, 60.23; H, 3.79; N, 7.02. Found: C, 60.51; H, 3.92; N, 6.96.

The infrared absorption spectrum showed the absence of any significant absorption in the carbonyl region and a definite absorption at 2.94 μ assigned to the indole NH; λ_{max} (log ϵ) 258 (4.36), 268* (4.33), 330 (4.29), 405 (3.82), and 440* mμ (3.49).

3,4-Dimethoxyindolo[2,3-*a*]acridizinium (VIII) Perchlorate.—Starting with 0.8 g. of the pyridoindolecarboxaldehyde and using 2,3-dimethoxybenzyl bromide[14] instead of 3-methoxybenzyl bromide, but otherwise following the procedure used for making the 3-methoxy derivative VII, the desired 3,4-dimethoxyindoloacridizinium perchlorate VIII was obtained as a red-brown product, m.p. about 290° dec.; yield, 1.41 g. (81%). An analytical sample, prepared by recrystallization from acetonitrile or acetonitrile–ether, was orange, m.p. 313–314°; λ_{max} (log ϵ) 260 (4.53), 290 (4.37), 359 (4.50), 385* (4.17) and 480 mμ (3.90).

Anal. Calcd. for $C_{21}H_{17}N_2ClO_6$: C, 58.82; H, 4.00; N, 6.53. Found: C, 58.93; H, 4.05; N, 6.53.

The infrared absorption spectrum showed no significant absorption in the carbonyl region but a strong absorption at 2.96 μ, assigned to indole NH.

3-(3,4,5-Trimethoxybenzoxy)-4-methoxybenzaldehyde (X).—Isovanillin[15] (3.0 g.) was dissolved in freshly distilled pyridine and the solution cooled and stirred vigorously while a slight excess of 3,4,5-trimethoxybenzoyl chloride[16] was added slowly in small portions. After the solution had been kept for several hours at room temperature, the pasty mixture was poured into 2 l. of 3 *N* hydrochloric acid containing some ice. The precipitate was collected, washed with water, and dried, giving 5.5 g. (81%) of a slightly yellow colored solid, m.p. 145–150°, that was pure enough for the next step. The analytical sample formed irregular crystals, m.p. 158–160°, from benzene–petroleum ether (60–90°).

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.88; H, 5.17.

(14) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **127**, 1434 (1925).

(15) A. Lovecy, R. Robinson, and S. Sugasawa, *ibid.*, 817 (1930).

(16) W. H. Perkin, Jr., and C. Weizmann, *ibid.*, **89**, 1649 (1906).

3-(3,4,5-Trimethoxybenzoxy)-4-methoxybenzyl Alcohol (XI).—A pasty suspension of 3.0 g. of the aldehyde in methanol was added in small portions to a cooled solution (5%) containing 1 g. of sodium borohydride in methanol. After the reaction was complete the excess hydride was destroyed by dropwise addition of dilute sulfuric acid. The precipitated alcohol was collected, washed with water, and dried; yield, 2.5 g. (82%); m.p. 120–125°. The colorless alcohol formed irregular crystals from benzene–petroleum ether, m.p. 128–129°.

Anal. Calcd. for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.46; H, 5.70.

3-(3,4,5-Trimethoxybenzoxy)-4-methoxybenzyl Bromide (XII). A well stirred suspension of the alcohol XI (2.0 g.) in dry ether (100 ml.) was maintained at 0° and treated dropwise with 1.0 g. of phosphorus tribromide. The mixture was allowed to stand overnight at room temperature, and then shaken repeatedly with cold water until free from acid. The ethereal solution was dried, the ether evaporated, and the residue crystallized from benzene–petroleum ether as colorless nodules; m.p. 112–113°; yield, 1.7 g. (74%).

Anal. Calcd. for $C_{18}H_{19}O_6Br$: C, 52.57; H, 4.66. Found: C, 52.56; H, 4.71.

2-Methoxy-3-(3,4,5-trimethoxybenzoxy)indolo[2-3-*a*]acridizinium (IX) Perchlorate.—One gram of the pyridoindole carboxaldehyde IV was quaternized with XII in the usual way. To the crude quaternary salt in 25 ml. of methanol, 10 ml. of concentrated hydrochloric acid was added, and cyclization carried out as usual, except that heating was continued for 1 hr. instead of the usual 15 min. The acid was evaporated, the resulting oil taken up in methanol and precipitated as the perchlorate by the addition of 20% perchloric acid. The oily perchlorate was washed with water and recrystallized from acetonitrile–ether. The product which showed some signs of decomposition during recrystallization consisted of a red-brown powder; m.p. 203–209° dec.; yield, 2.26 g. (73%). Alcoholic solutions of the product showed a very strong yellow-green fluorescence, and the infrared spectrum showed an absorption in the carbonyl region at 5.75 μ and another absorption in the 2.90-μ region attributed to the NH peak.

Anal. Calcd. for $C_{30}H_{25}N_2ClO_{10} \cdot H_2O$: C, 57.47; H, 4.34; N, 4.47; OCH_3, 19.80. Found: C, 57.41; H, 4.30; N, 4.49; OCH_3, 20.43.

The Solvolysis of 4α- and 4β-Methylcholesteryl *p*-Toluenesulfonate[1a]

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Received April 25, 1963

The hydrolysis of 4α-methylcholesteryl *p*-toluenesulfonate (IX) in 60% aqueous acetone in the presence of potassium acetate yields 55% of 3α,5α-cyclo-4α-methylcholestan-6β-ol (XVIII) together with minor amounts of diene and unrearranged parent alcohol X. The type and distribution of products obtained indicate that this solvolytic reaction is completely analogous to that of cholesteryl *p*-toluenesulfonate. In contrast, under the same conditions, 4β-methylcholesteryl *p*-toluenesulfonate (XVI) yields 80% of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX), 5–7% of the ring-contracted alcohol 3β-(1β-hydroxyethyl)-Δ^5-A-norcholestene (XIX) and a trace of unrearranged parent alcohol (XVII); no 3α,5α-cyclosterol is obtained. Elucidation of the structures of these products and a discussion of factors which may account for the striking difference in solvolytic behavior of IX and XVI are presented.

The 3β-hydroxy-Δ^5 system of steroids represents a useful substrate for the study of homoallylic participation in solvolytic reactions. Under nonacidic conditions, the solvolysis of ester derivatives of this system yields the corresponding homoallylic rearrangement product, namely, a 3α,5α-cyclo-6β substituted steroid.[2] Substantial rate enhancement also is observed[3]; for example, the relative rates of acetolysis at 100° of cholestanyl and cholesteryl *p*-toluenesulfonates are 1:100. Rate acceleration and stereospecific formation of products in the cholesteryl system may be explained in terms of an activation process involving ionization at C-3 facilitated by participation of the C-5–C-6 double bond. The extent of participation in the transition state for ionization depends upon how effectively the p-orbital at C-5 of the double bond can overlap with the developing p-orbital at C-3. Simonetta and Winstein[4] have applied semiempirical molecular orbital calculations to the cholesteryl cation with the important results that (a) at a normal C-3–C-5

(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, 1963.

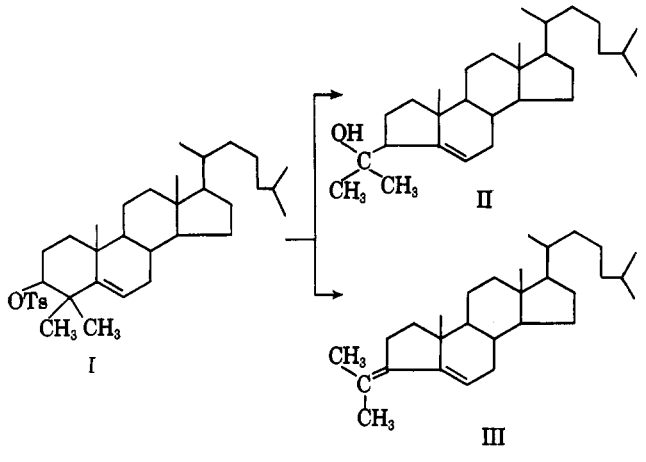
(2) E. S. Wallis, E. Fernholtz, and F. T. Gephardt, *J. Am. Chem. Soc.*, **59**, 137 (1937).

(3) S. Winstein and R. Adams, *ibid.*, **70**, 838 (1948).

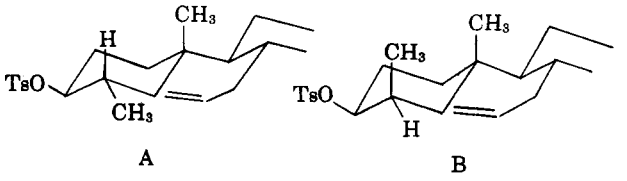
(4) M. Simonetta and S. Winstein, *ibid.*, **76**, 18 (1954).

distance of 2.5 Å. electron delocalization may lead to appreciable stabilization, and (b) with moderate compression of the C-3–C-5 distance, the 1,3-overlap integral increases significantly.

With a view toward learning the effect of substituents at C-4 upon the 1,3-electron delocalization in this system, a study of the products[5a] and kinetics[5b] of solvolysis of 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) was undertaken. The rate of solvolysis of this compound was found to be about four times faster than that of cholesteryl *p*-toluenesulfonate, while the saturated analog, 4,4-dimethylcholestanyl *p*-toluenesulfonate, solvolysed at a rate only one-third greater than cholestanyl *p*-toluenesulfonate. These results clearly indicate participation of the double bond in I in the rate-limiting ionization step. Two further inferences may also be drawn. Firstly, contrary to a "flattened A-ring" which has been proposed by Allinger[6] as a means of relieving the 1,3-diaxial methyl interaction between the methyl groups at C-4 and C-10 in 4,4-dimethyl-3-keto steroids no substantial flattening can exist in I. If such flattening did occur, participation would be precluded due to the increased C-3–C-5 distance, and the rate of solvolysis of I would, therefore, resemble that of cholestanyl *p*-toluenesulfonate. Secondly, the rate enhancement observed for I over cholesteryl *p*-toluenesulfonate may be considered to arise from either a steric effect of the geminal dimethyl group at C-4, involving a Thorpe–Ingold[7] type compression of the C-3–C-5 distance and thus allowing better overlap, or the methyl groups may stabilize the homoallylic ion by an inductive mechanism. A further point of interest in the solvolysis of 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) is the observation that no *i*-steroid is formed but only ring-contracted diene III (70%) and ring-contracted alcohol 3-(2-hydroxypropyl)-Δ⁵-A-norcholestene (II) (20%).[5a]

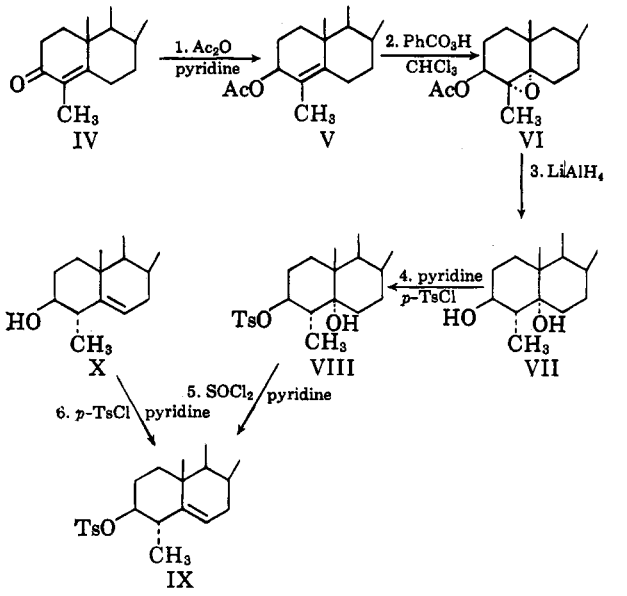


An obviously pertinent extension of this study is the investigation of the solvolytic behavior of the isomeric 4α- and 4β-methylcholesteryl *p*-toluenesulfonate esters, IX and XVI, respectively, which is reported in this paper. 4β-Methylcholesteryl *p*-toluenesulfonate (XVI) resembles 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) in that the 1,3-diaxial interaction between the C-4 and C-10 methyl groups is present. 4α-Methylcholesteryl *p*-toluenesulfonate (IX) does not possess this interaction, and, in this sense, resembles cholesteryl *p*-toluenesulfonate. These stereochemical relationships are depicted by structures A and B.



Preparation of Compounds.—4α-Methylcholesteryl *p*-toluenesulfonate (IX) was prepared *via* the steps outlined in Chart I. Dehydration of the 4α-methylcholestane-3β,5α-diol 3-*p*-toluenesulfonate (VIII) with thionyl chloride in pyridine was found to be the best method of preparation for compound IX. The direct tosylation of the parent alcohol, 4α-methylcholesterol (X), gave low yields of IX. 4α-Methylcholesterol (X) has been prepared by Julia and Lavaux[8] by dehydration of the 3-monoacetate of VII followed by saponification. An alternative method for the preparation of X is *via* sodium borohydride reduction of 4-methyl-Δ³·⁵-cholestadien-3-ol acetate.[9] A maximum yield of 12% of X was achieved by this method. The

CHART I



position of the double bond in IX was established to be at C-5–C-6 rather than the *a priori* more likely C-4–C-5 position (the hydrogen at C-4 and the hydroxyl group at C-5 are *trans* coplanar in VIII) by the following data. Firstly, the n.m.r. spectrum[10] showed the absence of CH_3–C=C in the 8.3-τ region and the presence of one vinyl proton 4.70 τ. Secondly, the material was levorotatory which is characteristic of

(5)(a) R. M. Moriarty and E. S. Wallis, *J. Org. Chem.*, **24**, 1274, 1987, (1959); (b) W. J. A. Vanden Heuvel, R. M. Moriarty, and E. S. Wallis, *ibid.*, **27**, 725 (1962).

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

(7) For a recent discussion of the Thorpe–Ingold effect see: P. von R. Schleyer, *ibid.*, **83**, 1368 (1961).

(8) S. Julia and J. P. Lavaux, *Compt. rend.*, **254**, 3702 (1962).

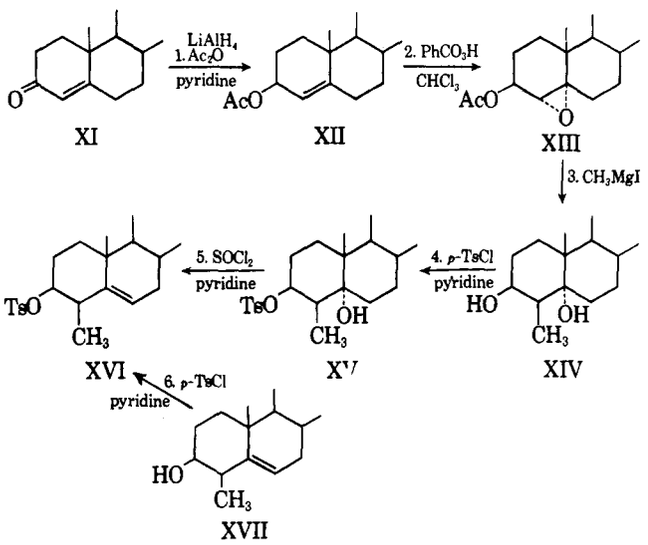
(9) Unpublished experiment of J. A. Feeley. This synthesis will be reported in a future paper dealing with the mechanism of sodium borohydride reduction of dienol acetates.

(10) All peak positions are reported in τ-values relative to tetramethylsilane as internal reference. Carbon tetrachloride is used as solvent unless otherwise stated.

Δ^5 steroids.[11] Thirdly, the same compound was obtained by tosylation of the parent alcohol X prepared by the borohydride reduction of the enol acetate mentioned before[9] or *via* the method of Julia and Lavaux.[8] The direction of dehydration in this case is probably determined by the relative stabilities of the products. In the cholesteryl series, infrared olefinic stretching frequencies indicate that the Δ^5 double bond (1690 cm.$^{-1}$) is more stable than the Δ^4 double bond (1657 cm.$^{-1}$).[12]

The synthesis of 4β-methylcholesteryl *p*-toluenesulfonate (XVI) is outlined in Chart II. Again the final step in this synthesis is the thionyl chloride–pyridine dehydration of the hydroxy tosylate precursor. 4β-Methylcholestane-3β,5α-diol (XIV) has been previously prepared by Julia and Lavaux,[13] who also transformed the 3-monoacetate derivative *via* dehydration and saponification into 4β-methylcholesterol (XVII). Δ^4-Cholesten-3β-ol-acetate (XII) (allocholesteryl acetate) was prepared in 60% yield by lithium aluminum hydride reduction of cholestenone (XI) followed by acetylation and separation from epiallocholesteryl acetate by chromatography. The highly stereoselective α-epoxidation of XII has been discussed by Henbest and Wilson.[14] The stereochemistry of the Grignard reaction product XIV is reasonable in terms of analogy with the course of lithium aluminum hydride reduction of epoxide XIV to yield only cholestane-3β,5α-diol.[14] Tosylate XVI also could be obtained from 4β-methylcholesterol (XVII) by direct treatment with *p*-toluenesulfonyl chloride in pyridine, although in much inferior yields compared with the previously described method.

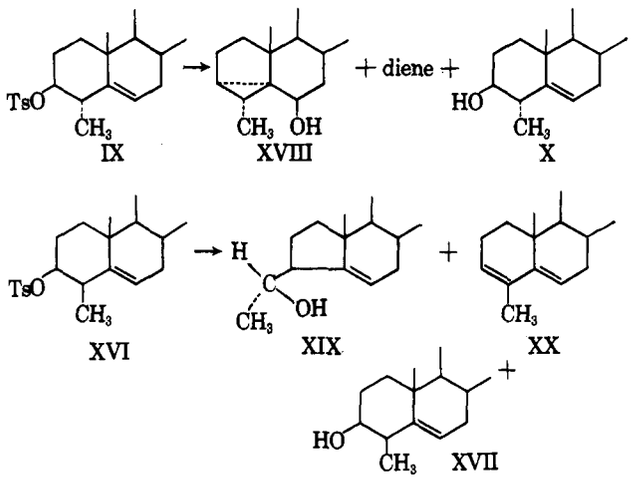
CHART II



Experimental Results

The products resulting from the buffered hydrolysis of 4α-methylcholesteryl *p*-toluenesulfonate (IX) and 4β-methylcholesteryl *p*-toluenesulfonate (XVI) are outlined in Chart III.

CHART III



The crude product from the hydrolysis of XVI was readily separable by chromatography into an olefinic part and alcoholic part. The crystalline olefinic fraction accounted for 80% of the product and was identified as 4-methyl-$\Delta^{3,5}$-cholestadiene (XX); m.p. 73–74°; $[\alpha]_D$ −100°; λ_{max}^{EtOH} 231 sh (ϵ 15,800), 239 (20,000), 247 mμ sh (11,000).[13] The alcohol part, upon rechromatography, yielded 4–7% of rearranged alcohol XIX, $C_{28}H_{48}O$, m.p. 113–14°, $[\alpha]_D$ −40°. A trace of a second alcohol was also obtained which proved to be 4β-methylcholesterol (XVII). Alcohol XIX was immediately recognized as not being an *i*-steroid due to the presence of unsaturation (tetranitromethane[15] and bromine in carbon tetrachloride) and also due to the negative sign of its rotation (the 3β-ol-Δ^5 → 3α,5α-cyclo-6β-ol transformation is invariably accompanied by a change in the sign of optical rotation from a negative value to a positive value).[16] The n.m.r. spectrum of XIX showed absence of cyclopropyl protons in the 9.5–9.9-τ region. The vinyl proton at C-5 was observed at 4.30 τ and the (CH_3)–CH–OH methyl appeared as a doublet at 8.76 τ. Oxidation of XIX with chromium trioxide in pyridine yielded a crude product which possessed infrared absorption (CCl_4) at 5.83 and 5.93 μ. This result corresponds to oxidation of the ethanol side chain at C-3 to a mixture of the unconjugated and conjugated carbonyl derivative. Chromatographic separation yielded the pure latter compound, λ_{max}^{EtOH} 257 mμ (ϵ 13,600). The properties of this material are in agreement with those reported for 3-acetyl-Δ^4-A-norcholestene.[17] Mild acid-catalyzed rearrangement of XIX (filtration over acidic alumina) afforded 4-methyl-$\Delta^{3,5}$-cholestadiene (XX). These data are taken to establish the structure of XIX as 3β-(1β-hydroxyethyl)-Δ^5-A-norcholestene. The stereochemistry of the hydroxyl group of the ethanol side chain is tentatively assigned the β-configuration (using the C-20 pregnane convention). This assignment is based upon the presumed stereochemistry of attack of solvent on the intermediary homoallylic ion (see discussion section).

(11) S. Bernstein, E. M. Hicks, Jr., D. M. Clark, and E. S. Wallis, *J. Org. Chem.*, **11**, 646 (1946).
(12) R. N. Jones and F. Herling, *ibid.*, **19**, 1252 (1954).
(13) S. Julia and J. P. Lavaux, *Compt. rend.*, **251**, 733 (1960).
(14) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).
(15) Although it has been reported[15b] that cyclopropyl containing compounds give a faint yellow color with tetranitromethane, the conditions for use of the reagent in the present study were standardized based upon the production of no color with 3α,5α-cyclocholestan-6β-ol.
(16) This conclusion is based upon an examination of the optical rotations of numerous 3α,5α-cyclo-6β substituted steroids.
(17) S. Julia, J-P Lavaux, S. R. Pathak, and G. H. Whitham, *Compt. rend.*, **256**, 1537 (1963).

Julia, *et al.*,[17] have also reported, in preliminary form, results on the hydrolysis of 4β-methylcholesteryl *p*-toluenesulfonate (XVI). They have found the same products and amounts of products as obtained in the present investigation. They assign, without explanation, the β-configuration to the hydroxyl group of the hydroxyethyl side chain of XIX. Stereoselective synthesis is required to establish this point of stereochemistry.

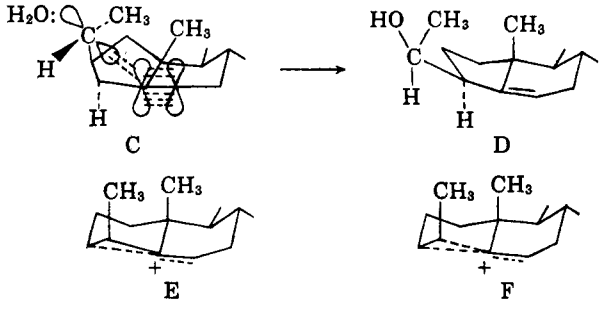
The products from the solvolysis of IX were separated into the olefinic component (20%) and the alcohol part (75%) by means of chromatography. The ultraviolet spectrum of the dienic fraction was similar to that of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX), although this material failed to crystallize. Rechromatography of the alcoholic fraction yielded two alcohols. The first of the alcohols XVIII, $C_{28}H_{48}O$, m.p. 101–102°, $[\alpha]D$ +18°, gave no indication of being unsaturated in the tetranitromethane test[15] and bromine in carbon tetrachloride test, and showed no olefinic absorption in the infrared. The saturated nature of XVIII, together with its positive sign of rotation and mode of formation indicated an *i*-steroidal structure for this substance. Further, chemical evidence supporting this conclusion came from the oxidation of XVIII with chromium trioxide–pyridine to a ketone with infrared carbonyl absorption (CCl_4) at 5.91 μ and no ultraviolet absorption above 225 mμ. These properties are consonant with the properties expected for the corresponding *i*-ketone. The structure of XVIII is therefore assigned as 3α,5α-cyclo-4α-methylcholestane-6-β-ol. The second alcohol was identified as the unrearranged parent compound, namely, 4α-methylcholesterol (X), by comparison with a known sample.

Discussion of Results

It is clear from the identity and distribution of the products formed in the solvolysis of 4α- and 4β-methylcholesteryl *p*-toluenesulfonate (IX and XVI) that the configuration of the C-4 methyl group plays a key role in the product forming step. A reasonable description of the influence of the methyl group may be achieved by considering (a) steric strain present in the ground states of IX and XVI, (b) steric and electronic factors contributing to the stability of the corresponding homoallylic ions derived from IX and XVI, and, (c) the steric factors present in the observed and possible products.

The solvolysis of 4α-methylcholesteryl *p*-toluenesulfonate (IX) is completely analogous to that of cholesteryl *p*-toluenesulfonate. This is not unexpected due to the neutral steric influence of the equatorial methyl group at C-4. The corresponding homoallylic ion in this case should possess enhanced stability due to the inductive effect of the methyl group. The *i*-steroid XVIII which is obtained is no more strained than *i*-cholesterol itself. No conceivable alternative path of decomposition for the intermediary ion is open; ring contraction to a five-membered A-ring structure is energetically unrewarding both in terms of strain energy and electronic stability; *i.e.*, transformation of the homoallylic ion to an open secondary carbonium ion is accompanied by a considerable decrease in electronic stability with no compensating gain in steric stability.

The solvolytic behavior of XVI is comparatively more complex. The ground state of XVI is strained to the extent of about 3.7 kcal./mole due to the 1,3-diaxial C-4–C-10 dimethyl interaction.[6] Both the transition state for ionization and the intermediary homoallylic ion retain this steric interaction. Formation of the ring-contracted alcohol is clearly accompanied by a favorable free energy change due to removal of this steric destabilization. Furthermore, obtention of one alcohol is in agreement with stereospecific attack upon the unsymmetrical homoallylic ion C as indicated (C → D).



Also contributors E and F must be considered in describing the homoallylic intermediate. Formation of unrearranged parent alcohol may derive from an unsymmetrical contributor such as E.

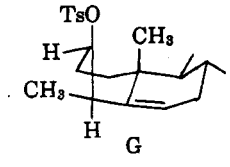
The formation of 80% of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX), to a first approximation, may be considered as a simple loss of a proton from the intermediary homoallylic ion. Two further modes of formation which cannot be excluded by the present data are (a) the corresponding *i*-steroid forms but undergoes dehydration under the reaction conditions, and (b) the diene originates by partial dehydration *in situ* of XIX.

The *i*-steroid, 3α, 5α-cyclo-4β-methylcholestan-6β-ol, would be expected to possess high reactivity. A 3α, 5α-cyclosterol is estimated to be about 6 kcal./mole less stable than the corresponding Δ^5-sterol.[18] In addition, 3α, 5α-cyclo-4β-methylcholestan-6β-ol would be further destabilized to the extent of 3.7 kcal./mole[6] due to the 1,3-diaxial methyl interaction and to at least 4 kcal./mole due to the additional interactions of the axial hydroxyl group with the two methyl groups. If equilibration could take place under the reaction conditions employed for the solvolysis, rearrangement of the i-steroid to diene XX would be possible. At present, this possibility cannot be experimentally tested due to the unavailability of 3α,5α-cyclo-4β-methylcholestan-6β-ol. The second conceivable origin of diene XX may be from dehydration of initially formed XIX *via* Wagner-Meerwein rearrangement followed by proton loss. This path is considered due to the facts that (a) such a reaction has been carried out, albeit under acidic condition, (b) XIX undergoes mutarotation at room temperature in chloroform solution, and (c) the ultraviolet spectrum of XIX upon standing develops absorption typical of diene XX. These results point to a facile dehydration of XIX to XX. Such a dehydration could also occur under the solvolytic conditions used for its formation. This reaction is currently under investigation.

A basically different explanation for predominant diene formation is that the ground state conformation of the A-ring of 4β-methylcholesteryl *p*-toluenesulfonate (XVI) may exist in a boat form (G). Such a confor-

(18)(a) C. W. Shoppee and D. F. Williams, *J. Chem. Soc.*, 2488 (1956); (b) C. W. Shoppee and G. H. R. Summers, *ibid.*, 3361 (1952).

mational change replaces the 1,3-dimethyl interaction by a 1,4-diaxial tosyloxy-methyl interaction and two sets of eclipsed hydrogen interactions at C-1 and C-2. Assuming that A-values[19] may be applied in this system, we may compare the A-value for tosyloxy, variously estimated at 0.6, 0.7, and less likely 1.7 kcal/mole, with the corresponding A-value[19] for methyl of 1.5–1.9 kcal./mole. Furthermore, the conformational equilibria involving 1,3-diaxial dimethyl have an interaction energy of 3.7 kcal./mole[6] while the corresponding value for methyl hydroxyl is 2.2–2.4 kcal./mole (the A-value for hydroxyl is 0.4–0.9 kcal./mole). The value for the two eclipsed sets of hydrogens at C-1 and C-2 is about 1.8 kcal./mole. Consideration of these energy values 3.7 kcal./mole for a chair A-ring and about 4.0 kcal./mole for a boat A-ring indicate that discussion of the mechanism of solvolysis of 4β-methylcholesteryl *p*-toluenesulfonate (XVI) in terms of a boat form A-ring is not unwarranted. The value of such a formulation is



that the *trans* coplanar relationship of the C-3 tosyloxy group and C-4 hydrogen presents the requisite stereochemistry for elimination. Furthermore, hydrogen participation may occur in the activation step for ionization. That such participation occurs and provides substantial anchimeric assistance is indicated by the relative rates of methanolysis at 35° for cholestanyl, epicholesteryl, and cholesteryl *p*-toluenesulfonates, 1:15:100.[20] The proposal of a boat form A-ring for XVI and the rejection of a boat form A-ring for 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) (see introduction) is not inconsistent in that one methyl group at C-4 in the geminal dimethyl case is always axially oriented and thus destabilized by interactions with protons on the α-side of the A-ring.

Experimental[11]

4-Methylcholestenone (IV) was prepared by the method of Ringold and Malhotra[22] in 25% yield and had m.p. 102–103°, $[\alpha]_D$ +108° (*c* 1), λ_{max}^{EtOH} 251 mμ (ε 15,200).

4-Methyl-Δ⁴-cholesten-3β-ol Acetate (V).—To a stirred slurry of 5.0 g. of lithium aluminum hydride in 300 ml. of 1:1 ether–tetrahydrofuran at reflux, 10 g. of 4-methylcholestenone, dissolved in 150 ml. of ether, was added dropwise over 0.5 hr. The reaction mixture was kept at reflux for 2 hr. Excess reducing agent was decomposed by addition of acetone followed by water. Extraction with ether, drying, and concentration under reduced pressure yielded 10 g., m.p. 132–134°; recrystallization from acetone yielded 8.0 g., m.p. 151–152° (lit.[8] 152°).

Acetylation of this material with acetic anhydride–pyridine yielded 7.0 g. of acetate, m.p. 108–111° (from acetone), $[\alpha]_D$ +40° (*c* 1) (lit.[8] 111°, $[\alpha]_D$ +45°).

4α,5α-Oxido-4β-methylcholestan-3β-ol Acetate (VI).—To a solution of 4.4 g. (10 mmoles) of compound V in 60 ml. of benzene was added a solution of 13 mmoles of perbenzoic acid in chloroform at room temperature. After 8 hr. at room temperature, an additional 100 ml. of benzene was added, and the resulting solution was washed with a solution of 25% aqueous sodium carbonate followed by washing with water. The dried benzene solution was concentrated to dryness *in vacuo*. The resulting oil, 4.3 g., showed no tendency to crystallize. Chromatography on unactivated Merck neutral alumina, 140 g., yielded two crystalline products. Elution with pentane–benzene (8:2) yielded 600 mg., of m.p. 80–81°, which may be the corresponding 4β,5β-oxide, but this material was not further investigated. Elution with pentane–benzene (1:1, 1.3 l.) yielded product which after recrystallization from acetone afforded 1.05 g. of the desired oxide VI, m.p. 132–34°, $[\alpha]_D$ +78° (*c* 1) (lit.[9] 131°, $[\alpha]_D$ +80°).

4α-Methylcholestane-3β,5α-diol (VII).—To a stirred slurry of 0.6 g. of lithium aluminum hydride in 100 ml. of ether at reflux was added 1.2 g. of compound VI in 50 ml. of ether. After 2 hr. at reflux, 50 ml. of tetrahydrofuran was added, and the reaction was kept at reflux for an additional 2 hr. At the end of this period, aqueous acetone was added and the solution was extracted with ether–benzene (1:1). Concentration of the dried combined extracts yielded 1.2 g. of crystalline solid. Recrystallization from ethanol yielded 0.90 g., m.p. 172–173° (lit.[9] 171°).

4α-Methylcholesteryl *p*-Toluenesulfonate (IX).—Compound VII (0.90 g.) was dissolved in 4 ml. of purified pyridine by warming. After cooling to 20°, 0.90 g. of *p*-toluenesulfonyl chloride was added, and the solution was swirled for about 2 min., whereupon the reaction mixture solidified. It was kept at room temperature for 12 hr. Then an additional 10 ml. of pyridine was added, the solution was cooled to 0°, and 2.3 ml. of thionyl chloride was added dropwise with stirring. The reaction mixture was kept at 0° for 15 min. and then diluted with 100 ml. of ether. The ether solution was cautiously treated with ice to decompose the excess thionyl chloride, washed with saturated sodium bicarbonate and water, dried, and concentrated to dryness *in vacuo*. The crude crystalline product was kept at 45° and 0.001 mm. for 15 min. The product was recrystallized from rigorously dried acetone and yielded 750 mg. of the *p*-toluenesulfonate ester IX, m.p. 121–122° dec., $[\alpha]_D$ −3° (*c* 0.4). The infrared spectrum (CCl_4) possessed absorption bands at 8.40 and 8.46 μ which are characteristic of the *p*-toluenesulfonate ester group. The analytical sample was prepared by recrystallization from acetone.

Anal. Calcd. for $C_{35}H_{54}O_3S$: C, 75.73; H, 9.79. Found: C, 75.71; H, 9.70.

Δ⁴-Cholesten-3β-ol Acetate (XII).—A solution of 2.5 g. of cholestenone in 30 ml. of ether and 30 ml. of tetrahydrofuran was added dropwise to a stirred slurry of 0.8 g. of lithium aluminum hydride in 80 ml. of ether. The reaction mixture was heated to reflux and kept at reflux for 1 hr. The product was isolated in the usual way and acetylated directly with 4 ml. of acetic anhydride in 10 ml. of pyridine. A gum resulted which was chromatographed on 60 g. of neutral alumina. Elution with hexane–benzene yielded 1.0 g., m.p. 78–79°. Recrystallization from acetone yielded 0.74 g., m.p. 81–82° (lit.[23] 85°).

4α,5α-Oxidocholestan-3β-ol Acetate (XIII).—This material was prepared in 60% yield by the epoxidation of XIII according to the method of Henbest and Wilson[14] and had m.p. 115–117°.

4β-Methylcholestane-3β,5α-diol (XIV).—To a stirred solution of 4α,5α-oxidocholestan-3β-ol acetate (XIII) (11 g.) in 130 ml. of anisole at 60°, a ninefold molar excess of methylmagnesium iodide in ether was added dropwise. The reaction was stirred overnight at 60°. At the end of this period it was cautiously added to 0.5 l. of acetic acid–water solution (1:1). This mixture was heated on the steam bath for 10 min. and then thoroughly extracted with ether. The ether solution was washed with saturated sodium bicarbonate solution and water. The dried ether solution was concentrated to dryness *in vacuo* and then heated at 50° and 0.001 mm. to remove the residual anisole. The crude crystalline product weighing 10 g. was chromatographed on 400 g. of Merck neutral alumina. Elution with chloroform yielded 6 g. of material of m.p. 179–182°. Recrystallization yielded 4.56 g., m.p. 181–183°, $[\alpha]_D$ +18° (*c* 1) (lit.[13] 181.5–182.5°, $[\alpha]_D$ +17°).

4β-Methylcholestane-3β,5α-diol 3-*p*-Toluenesulfonate (XV).—A solution of 2.0 g. of compound XIV in 3 ml. of dry pyridine was

(19) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc. New York, N. Y., 1962, pp. 236–237.

(20) L. C. King and M. J. Bigelow, *J. Am. Chem. Soc.*, **74**, 6238 (1952).

(21) 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. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrophotometer operating at 60.0 Mc. 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, New Jersey.

(22) H. J. Ringold and S. K. Malhotra, *ibid.*, **84**, 3402 (1962).

(23) H. McKennis and G. Gaffney, *J. Biol. Chem.*, **175**, 218 (1948).

cooled to 20°, and 2.0 g. of *p*-toluenesulfonyl chloride was added in one portion. The reaction was allowed to stand at room temperature overnight. An additional 7 ml. of dry pyridine was added, and a 1-ml. aliquot was removed for isolation of the hydroxy tosylate XV. Treatment of this aliquot with ice yielded solid which was collected and dried under high vacuum. Recrystallization from dry acetone yielded material, m.p. 97–98° dec., $[\alpha]_D$ −1.2° (*c* 0.4).

Anal. Calcd. for $C_{35}H_{56}SO_4$: C, 73.38; H, 9.85. Found: C, 73.43; H, 9.71.

4β-Methylcholesteryl *p*-Toluenesulfonate (XVI).—The pyridine solution of hydroxy tosylate XV was cooled to 0°, and 4 ml. of thionyl chloride was added dropwise with stirring. After 10 min. at 0°, 100 ml. of ether was added. The ether solution was cautiously treated with water. The ether was washed with a saturated solution of sodium bicarbonate followed by water. The ether solution was dried and concentrated to dryness *in vacuo* yielding a crystalline solid. Recrystallization from dry acetone yielded 1.4 g., m.p. 98–100° dec., $[\alpha]_D$ −77.8° (*c* 1).

Anal. Calcd. for $C_{35}H_{54}SO_3$: C, 75.73; H, 9.79. Found: C, 75.36; H, 9.53.

Hydrolysis of 4α-Methylcholesteryl *p*-Toluenesulfonate (IX).—A solution of 400 mg. of IX in 60 ml. of acetone and 10 ml. of water containing 400 mg. of potassium acetate was kept at reflux for 12 hr. Then most of the acetone was removed under reduced pressure. The remainder was extracted with ether; the ether solution was dried and concentrated to dryness *in vacuo* yielding 300 mg. of crystalline product. This material was chromatographed upon 5 g. of Merck neutral alumina. Elution with pentane yielded 60 mg. of oil which failed to crystallize. The ultraviolet spectrum of this oil was similar to that of XX. Further elution with benzene–ether (1:1) yielded 180 mg. of XVIII, m.p. 99–101°, $[\alpha]_D$ +18° (*c* 1). The analytical sample prepared by recrystallization from acetone had m.p. 101–102°.

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 83.90; H, 12.01.

Elution with chloroform afforded 60 mg. of crystalline material. Upon recrystallization from acetone, this material had m.p. 164–165°, $[\alpha]_D$ −16°, identical with a sample of 4α-methylcholesterol (X).

Hydrolysis of 4β-Methylcholesteryl *p*-Toluenesulfonate (XVI).—A solution of 2.0 g. of tosylate XVI was dissolved in 300 ml. of acetone and 50 ml. of water containing 2.1 g. of potassium acetate. This reaction mixture was kept at reflux overnight. The acetone was removed under vacuum, and the residue was thoroughly extracted with ether. The ether solution was dried and concentrated *in vacuo* to a gum, 1.4 g. Chromatography upon 60 g. of Merck alumina yielded 1.20 g. of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX), identified by comparison with a known sample. Further elution with benzene–ether (1:1, 3:7) gave 110 mg. of crystalline material which upon recrystallization from acetone yielded 90 mg. of XIX, m.p. 113–114°, $[\alpha]_D$ −40° (*c* 0.4).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 84.00; H, 12.30.

Further elution with chloroform gave 6 mg. of material identified as 4β-methylcholesterol (XVII) by comparison with a known sample prepared by the method of Julia.[13]

Chromium Trioxide–Pyridine Oxidation of IX.—To a chromium trioxide–pyridine complex, prepared by portionwise addition of 24 mg. of chromium trioxide to 0.25 ml. of pyridine, was added a solution of 24 mg. of IX in 0.25 ml. of pyridine. The reaction mixture was stored at room temperature overnight. Ice was added followed by water, and the final mixture was extracted with six portions of chloroform. The combined extracts were washed with dilute hydrochloric acid, a saturated solution of sodium bicarbonate, and finally with water. The organic layer was dried and concentrated to dryness under reduced pressure. The resulting gum, 27 mg., possessed infrared absorption (CCl_4) at 5.91 μ, and no ultraviolet absorption above 225 mμ. Chromatography upon neutral alumina (Merck) yielded 17 mg., m.p. 100–106°.

Anal. Calcd. for $C_{28}H_{48}O$: C, 84.35; H, 11.63. Found: C, 84.00; H, 11.82.

Chromium Trioxide–Pyridine Oxidation of XIX.—The required oxidizing complex was prepared by portionwise addition of 43 mg. of chromium trioxide to 0.50 ml. of pyridine. A solution of 43 mg. of XIX in 0.50 ml. of pyridine was added, and the reaction mixture was allowed to stand at room temperature overnight. Isolation of the product by the method used yielded a gum weighing 47 mg. This material possessed infrared absorption (CCl_4) at 5.83 and 5.93 μ (C=O in ratio of 2:5, respectively). Chromatography upon Merck basic alumina yielded 21 mg., m.p. 97–99°, λ_{max}^{EtOH} 257 mμ (ε 13,700).

Anal. Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.10. H, 11.40.

Dehydration of XIX.—A 9-mg. sample of XVIII in benzene was charged to a Woelm acid-washed alumina column. After 0.5 hr., elution with pentane yielded 5 mg., m.p. 71–72°, undepressed upon admixture with an authentic sample of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX).

Acknowledgment.—The authors wish to thank Prof. J. Rocek of this department for several illuminating discussions. Also, the invaluable assistance of Prof. P. von R. Schleyer of Princeton University is acknowledged for determining the n.m.r. spectra.

Electrophilic Substitution of the Benzenethiols. II. Acylbenzene- and Acyltoluenethiols[1,2]

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Received May 3, 1963

Acylarylthiols are prepared from arylthiol precursors. The new procedure comprises protection of the sulfur atom with a carboxymethyl group, acylation of the aromatic ring, and, finally, removal of the protective group.

An earlier paper[4] described a new method of obtaining monohaloarylthiols from arylthiols. A summary of the steps involved is provided by equation 1.

This scheme suggested an attractive means of obtaining acylarylthiols, compounds previously preparable only by tedious, classical methods, or by the use of a more complex approach.[5] A survey of the literature revealed no examples of the Friedel–Crafts acylation of arylmercaptoacetic acids, though Dann and Kokorudz[6] report formation of *p*-acetylphenylmercaptoacetic acid in very low yield by the action of hydrogen fluoride on phenylmercaptoacetic acid. In view of the ease with

$$C_6H_5SH \longrightarrow C_6H_5SCH_2CO_2H \xrightarrow[-H^+]{X^+} XC_6H_4SCH_2CO_2H \xrightarrow[H_2O_2]{H^+} XC_6H_4SH \quad (1)$$

(1) This work is the subject of Canadian, United States, and other patent applications.

(2) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(3) Arapahoe Chemicals, Inc., Boulder, Colo.

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