[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Transmission of Electrical Effects Through Homoallylic Systems. III. Synthesis and Kinetics of Solvolysis of 6-Methylcholesteryl *p*-Toluenesulfonate

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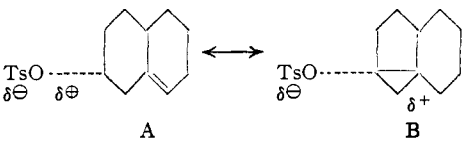
RECEIVED DECEMBER 16, 1957

The synthesis of 6-methylcholesteryl *p*-toluenesulfonate has been achieved and the rates of solvolysis of this ester in 90 volume per cent. aqueous dioxane at several temperatures have been measured. The first-order rate constant for solvolysis, extrapolated to 50.00°, is 1.36×10^{-3} sec.$^{-1}$, or 75 times the rate of the homologous cholesteryl *p*-toluenesulfonate and *ca.* 8840 times as fast as the saturated secondary ester, cholestanyl *p*-toluenesulfonate. The results are interpreted as further evidence for powerful anchimeric assistance to ionization provided by the C_5–C_6 π-electrons in this homoallylic system.

In a previous communication[1] a study of the kinetic behavior on solvolysis of the *p*-toluenesulfonate esters of a series of *p*-substituted 6-arylcholesterols was reported and interpreted as further evidence for the anchimerically-assisted ionization of cholesteryl systems; that is, the transition state for ionization of derivatives of cholesteryl sytems is pictured as a resonance hybrid of the canonical valence bond structures A and B.



A B

A comparison of the rates of solvolysis of these 6-arylcholesteryl *p*-toluenesulfonates relative to cholesteryl *p*-toluenesulfonate, however, led to the interesting conclusion that 6-aryl groups are actually less effective in stabilizing the ionization transition states than is 6-hydrogen. This result was somewhat unexpected in view of the tendency for aromatic rings to provide resonance stabilization to electron-deficient centers.

For various reasons to be discussed in detail below, it seemed of interest to study the kinetics of solvolysis of a 6-alkylcholesteryl *p*-toluenesulfonate. Accordingly, the synthesis of 6-methylcholesteryl *p*-toluenesulfonate was undertaken. This communication reports the synthesis of this ester and the results of a study of its behavior on solvolysis.

The synthesis of 6-methylcholesterol was first reported by Ushakov and Madaeva.[2] These authors obtained a methylcholestenol by the prolonged treatment of cholesterol α-oxide with the methyl Grignard reagent in refluxing benzene. This unsaturated alcohol was formulated as 6-methylcholesterol, solely by analogy with cholesterol. The synthesis of this compound by the method of Ushakov and Madaeva has been repeated by Fieser and Rigaudy.[3] These authors also prepared this same material by the sequence of reactions outlined below.

Thus addition of the methyl Grignard reagent to Ia furnished a diol IIa. The diol was acetylated to furnish a monoacetate IIb which was in turn dehydrated with either thionyl chloride–pyridine or acetic anhydride–sulfuric acid to furnish a cholestenyl acetate IIIb identical with that prepared by the Russian authors. The formation of identical 6-methylcholestenols by these two reaction sequences was presented by Fieser and Rigaudy as a convincing argument for the formulation of this compound as 6-methylcholesteryl acetate.

In the present work cholestan-3β-ol-6-one monoacetate (Ib) served as the starting material for the synthesis of 6-methylcholesterol. The addition of the Grignard reagent derived from methyl iodide furnished the earlier reported cholestan-3,6-diol (IIa). Monoacetylation furnished the 3-monoacetate IIb which was in turn dehydrated in excellent yields by the action of *p*-toluenesulfonic acid in refluxing acetic acid, or, in poorer yields, with phosphorus oxychloride in pyridine. 6-Methylcholesteryl acetate (IIIb) was isolated in only 33% yield by the latter method, a result quite consistent with the equatorial orientation assigned to the 6-alcohol function.[4] Saponification furnished the corresponding alcohol IIIa.

Attempts to prepare the *p*-toluenesulfonate ester directly from 6-methylcholesterol by the usual methods failed. Conditions which were effective in converting the previously reported 6-arylcholesterols to their esters[5] invariably produced only an oily material which could not be induced to crystallize. Accordingly, resort was had to the synthetic scheme outlined below. In this reaction sequence 6β-methylcholestan-3β,6α-diol (IIa) was treated with *p*-toluenesulfonyl chloride in pyridine to give, presumably, 6β-methylcholestan-3β,6α-diol mono-*p*-toluenesulfonate (IIc). This compound was not isolated. The reaction mixture was treated directly with thionyl chloride under conditions chosen so as to avoid prolonged contact of the resulting ester with the solvent. The reaction was complete in 10 minutes at 0°, and was worked up as described in the Experimental to furnish the desired 6-methylcholesteryl *p*-toluenesulfonate (IIIc).

Fieser and Rigaudy have formulated the diol IIa as 6α-methylcholestan-3β,6β-diol on the basis of two pieces of evidence. First, β-attack of the

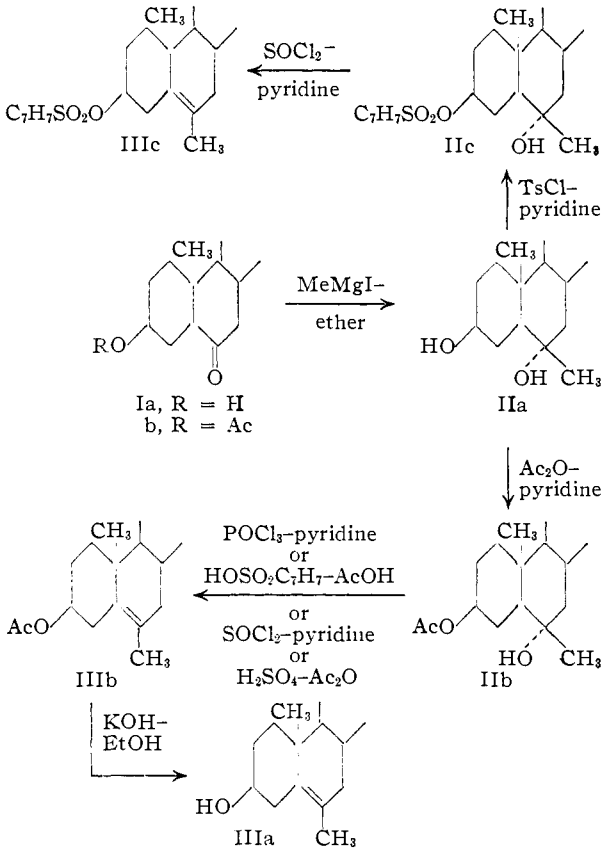
(1) R. A. Sneen, THIS JOURNAL, **80**, 3977 (1958).

(2) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem. (U.S.S.R.)*, **9**, 436 (1939); [*C. A.*, **34**, 3756 (1940)].

(3) L. F. Fieser and J. Rigaudy, THIS JOURNAL, **73**, 4660 (1951).

(4) Barton and co-workers have recently reported the phosphorus oxychloride–pyridine dehydration of 3β-methyl-3α-ol- and 3α-methyl-3β-ol cholestane. The former compound, with an axial alcohol function, gives an essentially quantitative yield of the endocyclic Δ^4-olefin. The latter compound (equatorial alcohol) gives a mixture of olefins containing some 3-methylene-cholestane; D. H. R. Barton, Ada S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

(5) R. A. Sneen, THIS JOURNAL, **80**, 3971 (1958).



Grignard moiety is presumed to be sterically unfavorable. However, for the reasons advanced in a previous publication,[5] we are inclined to feel that an analysis of the degree of steric hindrance in the corresponding α- and β-transition states cannot be made. A second argument presented by these authors for the assignment of a β- (or axial) orientation to the 6-alcohol function depends on an analysis of some of the molecular rotation data collected in Table I. The argument can be summarized in the following way: the substitution of a 6β-methyl group into cholestan-3β,5α-diol increases the levorotation. Therefore a 6α-methyl group should increase the dextrorotation (*cf.* cholestan-3β-5α-6α-triol and its 6β-isomer). Since the methyl diol under discussion is more dextrorotatory than cholestan-3β,6β-diol, it was formulated by these authors as 6α-methylcholestan-3β,6β-diol. If one grants the assumptions made above, however, the available data can be shown to be equally consistent with the alternative stereochemistry at C_6. Thus, since the methyl diol is more levorotatory than cholestan-3β,6α-diol, a logic similar to that used above requires that it be formulated as 6β-methylcholestan-3β,6α-diol. Actually the methyl diol has been tentatively formulated as 6β-methylcholestan-3β,6α-diol (IIa) both by analogy with the corresponding aryl diols[5] as well as on the basis of an analysis of the molecular rotation data[6] reproduced in Table I.

(6) The method used in analyzing these data, the details of which are soon to be published by J. H. Brewster, depends on an analysis of the polarizability of various substituents; thus the substitution of an alkyl or aryl group for the 6β-hydrogen atom in cholestan-3β,6α-diol is expected to exert a levorotatory effect on the molecular rotation.

TABLE I

OBSERVED AND CALCULATED MOLECULAR ROTATION VALUES

Compound	M_D Obsd.	Calcd.
Cholestan-3β,6β-diol[4]	+ 57	
Cholestan-3β,6α-diol[4]	+154	
Cholestan-3β,5α-diol[4]	+ 81	
6β-Methylcholestan-3β,5α-diol[4]	− 6.3	
6β-Methylcholestan-3β,6α-diol	+ 73	+ 78–+ 94
6α-Methylcholestan-3β,6β-diol	.....	+108–+114
6β-Phenylcholestan-3β,6α-diol[5]	+ 50	(+ 18–+ 48)
		(+ 34–+ 64)
6α-Phenylcholestan-3β,6β-diol[5]	.....	(+138–+168)
		(+147–+177)

The double bond in the dehydration product IIIb of 6β-methylcholestan-3β,6α-diol monoacetate and the derived methylcholestenol IIIa has been assigned to the Δ^5-position by Fieser and Rigaudy on the basis of its formation from both 6β-methylcholestan-3β,5α-diol and 6β-methylcholestan-3β,6α-diol monoacetate. Further evidence can be advanced for the formulation of this compound as 6-methylcholesterol as for the formulation of the *p*-toluenesulfonate ester described above as 6-methylcholesteryl *p*-toluenesulfonate: 1, the synthesis of both compounds involved dehydration under basic conditions, thereby restricting the double bond with a high degree of probability to either the endocyclic Δ^5- or Δ^6-location or to an exocyclic 6-methylene position; 2, the presence of an exocyclic methylene group in the alcohol is made improbable by its synthesis from the diol acetate under supposedly isomerizing conditions.[8] The infrared spectra of both the alcohol and ester are transparent in the region characteristic of methylene groups[9]; 3, the Δ^6-orientation is made improbable by the molecular rotation data[10] recorded in Table II; 4, the failure of attempts to synthesize the *p*-toluenesulfonate ester directly from the alcohol under standard conditions and the kinetic behavior of the *p*-toluenesulfonate ester (*vide infra*) readily can be understood in terms of the general theory of homoallylic steroidal systems with a Δ^5-double bond,[11] but would be surprising indeed for a compound possessing a geometrically unfavorable Δ^6-double bond; and 5, the nuclear magnetic resonance spectra of both the alcohol and of the ester are completely transparent in the region of vinyl hydrogen absorption.[12] Inspection of the spectra

Since an aryl group is more polarizable than is methyl[7] the observed greater levorotatory shift effected by the phenyl group as previously reported[5] seems to us a particularly cogent argument in favor of the assigned stereochemistry.

(7) See, for example, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 125 *et seq.*

(8) For pertinent references see H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, **76**, 467 (1954).

(9) N. Sheppard and D. M. Simpson, *Quart. Revs.*, **6**, 1 (1952).

(10) As in a preceding communication,[8] the assumption is made that the effect of a 6-alkyl substituent on the molecular rotations of both the Δ^5- and Δ^6-cholestenols would be to enhance any effect which the double bond might exert on the molecular rotations. Again the inner consistency of the molecular rotations of the 6-methylcholesterols and of the 6-arylcholesterols[5] containing more polarizable aryl groups argues strongly for a similar assignment of unsaturation in both series of compounds and, in particular, for a Δ^5-orientation.

(11) See ref. 1 for earlier references.

(12) L. H. Meyer, A. Saika and H. S. Gutowsky, THIS JOURNAL, **75**, 4567 (1953).

of cholesterol and of cholesteryl *p*-toluenesulfonate revealed that absorption due to the single vinyl hydrogen at C_6 in these compounds is quite distinctive, and therefore the absence of this type of absorption in the spectra of our 6-methylcholestenol and of the ester requires the double bond in these compounds to be tetrasubstituted, and, accordingly, situated at C_5–C_6.

TABLE II

COMPARISON OF MOLECULAR ROTATION VALUES

Compound	M_D	ΔM_D[a]
Cholestanol[b]	+93	...
Cholesterol[b]	−151	−244
Δ^6-Cholestenol[c]	−367	−460
6-Methylcholesterol	−185	−278
Cholesteryl *p*-toluenesulfonate[d]	−222	−315
6-Methylcholesteryl *p*-toluenesulfonate	−241	−334

[a] $\Delta M_D = M_D - M_{D\text{cholestanol}}$. [b] L. F. Fieser and Mary Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 216. [c] D. H. R. Barton and W. J. Rosenfelder, *Nature*, **164**, 316 (1949). [d] E. Bátyka, *Magyar Biol. Kutató Intéz et Mun Kái*, **13**, 334 (1941); [*C.A.*, **36**, 484 (1942)].

The kinetic results of this investigation are assembled in Table III. The solvent system used was 90 volume per cent. aqueous dioxane containing sufficient lithium acetate to react with the *p*-toluenesulfonic acid formed during solvolysis. The titrimetric rates were followed with standard aqueous potassium hydroxide to the phenolphthalein end-point, all of the runs being carried to at least 86% reaction. A polarimetric technique was also used to measure the rate of reaction at 24.5° and found to give a rate constant in essential agreement with the titrimetric rate constant at 25.00°. 6-Methylcholesteryl *p*-toluenesulfonate solvolyzes with good first-order kinetics.[13] The rate of solvolysis of 6-methylcholesteryl *p*-toluenesulfonate at 50.00° has been calculated from the experimental rate data at lower temperatures.

TABLE III

RATES OF SOLVOLYSIS OF 6-METHYLCHOLESTERYL *p*-TOLUENESULFONATE IN 9:1 VOLUME PER CENT. AQUEOUS DIOXANE

[ROTs] × 10^2	[LiOAc] × 10^2	T, °C.	k_1, sec.$^{-1}$	Method[a]	Reaction, %
1.43	1.82	39.96[b]	$4.36 \pm 0.06 \times 10^{-4}$	T	47–91
1.14	1.30	25.00[b]	$7.40 \pm .09 \times 10^{-5}$	T	22–92
0.812	1.41	20.05	$3.85 \pm .11 \times 10^{-5}$	T	27–86
1.14	1.30	24.5	$7.8 \pm .4 \times 10^{-5}$	P	
		50.00	1.36×10^{-3}	E	

[a] T = titrimetric; P = polarimetric; E = extrapolated. [b] $\Delta H^* = 21.4$ kcal., $\Delta S^* = -5.7$ e.u.

In Table IV are collected the extrapolated rate of solvolysis of 6-methylcholesteryl *p*-toluenesulfonate at 50.0° as well as the rates of some compounds reported in a previous communication relative to the rate of cholestanyl *p*-toluenesulfonate.[1] 6-Methylcholesteryl *p*-toluenesulfonate is seen to solvolyze at a rate 74.8 times as fast as its 6-hydrogen homolog. Thus the substitution of a 6-methyl group into cholesteryl *p*-toluenesulfonate confers significant stability ($\Delta\Delta F^* = 2.69$ kcal.) on the transition state of ionization of this system. The magnitude of this rate acceleration is emphasized by noting that 6-methylcholesteryl *p*-toluenesulfonate solvolyzes at a rate 8.84×10^3, or nearly four powers of ten faster than the saturated model compound cholestanyl *p*-toluenesulfonate. This rate factor corresponds to a difference in free energy of activation of 5.85 kcal.

TABLE IV

RELATIVE RATES OF SOLVOLYSIS OF STERYL *p*-TOLUENESULFONATES AT 50° IN 90 VOLUME PER CENT. AQUEOUS DIOXANE

Steryl *p*-toluenesulfonate	Relative rate
Cholestanyl[a]	1
6-Phenylcholesteryl[1]	37.6
Cholesteryl[1]	118
6-Methylcholesteryl	8.84×10^3

[a] $k_1 = 1.54 \times 10^{-7}$ sec.$^{-1}$, extrapolated from data in other solvents; see ref. 1.

That 6-methylcholesteryl *p*-toluenesulfonate solvolyzes by a process in which considerable positive charge is borne by C_6 would seem incontrovertible. These results are in complete accord with the predictions based on homoallylic theory[1] and serve to emphasize the degree to which the C_5–C_6 π-electrons are involved in the transition states of ionization of cholesteryl systems.

It is also instructive to compare the rate of solvolysis of 6-methylcholesteryl *p*-toluenesulfonate with that of 6-phenylcholesteryl *p*-toluenesulfonate; the 6-methyl derivative solvolyzes at a rate 235 times that of the phenyl compound. The observed order of effective stabilization in these systems is somewhat surprising.[14] If, as seems reasonable, 6-methylcholesteryl *p*-toluenesulfonate shows "normal" reactivity on solvolysis, the arylcholesteryl *p*-toluenesulfonates previously reported[1] must be considered "abnormal."

Several factors need to be considered as possible explanations for the unexpectedly low reactivity of the arylcholesteryl *p*-toluenesulfonates. First, the combined -I effects of the Δ^5-double bond and of the 6-aryl substituent should exert a depressive effect on the rates of solvolysis. However, it seems certain that this effect would be too small[15] to be responsible for the entire rate depression. Secondly, non-bonded steric interactions between a planar aryl ring at C_6 and the approaching atoms of the incipient three-membered ring might result in steric inhibition of resonance in the transition state; alternatively, it might result in a lengthening of the C_3–C_5 bond distance in the transition states of the arylcholesterols with respect to this distance in the unsubstituted or 6-methylcholesterols, and therefore a decrease in the effective stabilization imparted to the transition state by overlap between the partially empty orbital at C_3 with the π-electrons at C_5–C_6. In either case, models indicate

(13) Since the concentration of lithium acetate varied during the course of a single run by a factor of >4, any significant second-order reaction involving the concentration of lithium acetate should have revealed itself in drifting rate constants.

(14) For example, the relative rates of solvolysis of allyl, γ-methylallyl and γ-phenylallyl chlorides in 50% aqueous ethanol at 25° are reported to be 1.00:95:8800; see R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 786 (1956), for references and further data.

(15) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and L. J. Corse, THIS JOURNAL, **74**, 1113 (1952); A. Streitwieser, Jr., *Chem. Revs.*, **56**, 718 (1956).

that interactions of this type should not change greatly on proceeding from the starting material to the transition state.[16]

A third factor which might be invoked to explain the decreased reactivity of the arylcholesterols is the increased stabilization of the starting material due to the conjugation of the aryl ring with the C_5–C_6 π-electrons. Unless this ground state stabilization is accompanied by an equal or greater stabilization of the corresponding transition state, it would result in an increased energy of activation and, accordingly, a decrease in rate.[18]

That decreased opportunities for solvation of the transition states of the arylcholesteryl esters exist seems improbable since such factors should also be operative in the solvolysis of 6-methylcholesteryl *p*-toluenesulfonate in which considerable rate acceleration exists.

Finally, the interesting possibility exists that effective conjugation of the π-orbitals of the aryl ring with the homoallylic cation system is stereoelectronically[19] prohibited. Thus the distribution of electronic charge among the atoms C_3, C_5 and C_6 in the transition state may be such as to prevent the aryl π-electrons from being mesomerically transmitted to the electron-deficient area. Certainly the ground state *p* character of the C_5–C_6 π-electrons is being destroyed or at least altered as the C_3–C_5 bond is being formed. We are currently devising experiments to test this possibility.

Experimental

Preparation of Rate Solutions.—The procedure used was essentially identical with that already described for the arylcholesteryl *p*-toluenesulfonates.[1] However, the fast-solvolyzing methylcholesteryl *p*-toluenesulfonate made the use of sealed ampoules unnecessary. Instead, solutions of the ester were filtered directly into volumetric flasks. The flasks were, in turn, placed in a constant temperature bath accurate to ±0.1°.

Kinetic Measurements

A. Titrimetric Rates.—At appropriate time intervals aliquots (*ca.* 5 ml.) of the reacting solution were removed and quenched in *ca.* 8 ml. of carbonate-free water and titrated with dilute aqueous potassium hydroxide (*ca.* 2.0×10^{-2} *M*) to the phenolphthalein end-point. Infinity titers were measured after approximately ten half-lives. In one instance an infinity titer was measured also after greater than 20 half-lives and found to be essentially unchanged. The rate constants reported in Table III were determined from 6–12 experimental points. A typical kinetic run is illustrated in Table V.

TABLE V

SOLVOLYSIS OF 1.14×10^{-2} *M* 6-METHYLCHOLESTERYL *p*-TOLUENESULFONATE IN 90 VOLUME PER CENT. AQUEOUS DIOXANE AT 25.00°

$[LiOAc]_{initial} = 1.30 \times 10^{-2}$ *M*; $[KOH] = 1.980 \times 10^{-2}$ *M*

Time, sec.	KOH, ml.	k_1, sec.$^{-1} \times 10^5$
0	0.801	..
720	0.910	7.48
1620	1.093	7.50
2820	1.187	7.28
4320	1.367	7.36
6360	1.578	7.15
8400	1.740	7.43
10320	1.915	7.48
12660	2.074	7.47
15300	2.217	7.53
19380	2.397	7.34
30480	2.657	
∞	2.879	
	Average	7.40 ± 0.09

B. Polarimetric Rate.—A portion of the solution used in the kinetic run described in Table V was placed in a 2-dm. jacketed polarimetry tube through which water, constant to 24.65 ± 0.15°, was circulating. The optical rotation measured at the sodium D line was recorded periodically. The data were analyzed as previously described,[1] and are assembled in Table VI.

TABLE VI

SOLVOLYSIS OF 1.14×10^{-2} *M* 6-METHYLCHOLESTERYL *p*-TOLUENESULFONATE IN 90 VOLUME PER CENT. AQUEOUS DIOXANE AT 24.65 ± 0.15°

$[LiOAc]_{initial} = 1.30 \times 10^{-2}$ *M*; zero point = 354.73 ± 0.01

Time, sec.	α	k_1, sec.$^{-1} \times 10^5$
660	354.40 ± 0.00	..
1800	354.45 ± .00	8.0
4560	354.57 ± .01	7.6
6540	354.62 ± .01	7.5
8700	354.68 ± .00	7.7
10680	354.71 ± .01	7.3
12720	354.77 ± .00	8.1
15540	354.82 ± .02	8.3
18840	354.86 ± .01	8.4
∞	354.98 ± .00	
∞	354.98 ± .00	
	Average	7.8 ± 0.4

6β-Methylcholestan-3β,6α-diol (IIa) was prepared by the addition of a twofold excess of methylmagnesium iodide to the readily available cholestan-3β-ol-6-one acetate[20] (Ia) (6:1 molar ratio). To a previously prepared solution of the Grignard reagent (made up by the dropwise addition of a solution containing 12.5 g. of methyl iodide (0.088 mole) in 50 ml. of anhydrous ether to a stirred suspension of 1.750 g. (0.072 mole) of magnesium turnings in *ca.* 10 ml. of ether) was added a solution containing 5.327 g. (0.012 mole) of cholestan-3β-ol-6-one acetate (Ia) dissolved in *ca.* 50 ml. of anhydrous ether. The addition was made at a rate sufficient to maintain gentle reflux. The stirring was continued for about 2 hours after the addition had been completed, and the excess Grignard reagent then was decomposed by the dropwise addition of methanol. The precipitated salts were dissolved by the dropwise addition of 10% aqueous hydrochloric acid.

The ethereal solution was separated, washed once with water, and most of the ether was removed by boiling. Ethanol was added and the dropwise addition of water to the heated solution resulted in crystallization, furnishing 4.870 g. (96.9%) of 6β-methyl-3β,6α-cholestandiol (IIa), m.p.

(16) The ultraviolet spectra of the arylcholesterols[5] reveal that the C_5–C_6 double bond is conjugated with the aryl rings. The intensities of absorption (log ε 4.22 to 4.38) are comparable in magnitude to those of the corresponding styrenes.[17]

(17) For example, styrene has $\lambda_{max} \cong 245$, log ε 4.15; A. C. Cope and M. Burg, THIS JOURNAL, **74**, 168 (1952).

(18) The resonance energy possessed by styrene in excess of that of ethylbenzene has been calculated from heats of hydrogenation data to be 1.0 kcal., and from heats of combustion data as 2.9 kcal. See G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 80 and 98. Recently, however, Kreevoy and Taft have developed a quantitative approach to the problem of determining resonance energies. Their treatment takes into consideration polar and hyperconjugation contributions to the thermodynamic properties which are omitted in earlier treatments. They have calculated the extra energy of styrene compared to ethylbenzene as 5.8 kcal.; M. M. Kreevoy and R. W. Taft, Jr., THIS JOURNAL, **79**, 4016 (1957).

(19) The adverb is here used in the sense defined by E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956), footnote 3.

(20) B. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).

192.5–194°. The analytical sample was prepared by repeated crystallization from the same solvent, m.p. 194°, $[\alpha]^{27}D$ +17.5° (chloroform) (lit.[4] m.p. 193–194°, $[\alpha]D$ +20° (dioxane)).

Anal. Calcd. for $C_{28}H_{50}O_2$: C, 80.32; H, 12.06. Found: C, 80.16; H, 12.22.

6β-Methylcholestan-3β,6α-diol Monoacetate (IIb).—To a solution containing 6.375 g. (15.22 moles) of 6β-methylcholestan-3β,6α-diol (IIa) dissolved in 60 ml. of anhydrous pyridine was added 40 ml. of acetic anhydride. Reaction was allowed to proceed for 1 hour at steam-plate temperatures. After cooling to room temperature, the reaction mixture was poured into ice-water, and the resulting solid material was filtered, washed exhaustively with water and dried, furnishing 6.794 g. (95.5%) of crude 6β-methylcholestan-3β,6α-diol monoacetate (IIb), m.p. 161–161.75° (lit.[4] m.p. 166°). The crude monoester was used in the succeeding synthetic step without further purification.

6-Methylcholesteryl Acetate (IIIb). A. By the Action of Phosphorus Oxychloride in Pyridine.—To a solution containing 155 mg. of 6β-methylcholestan-3β,6α-diol monoacetate (IIb) in 2 ml. of anhydrous pyridine was added 2 ml. of phosphorus oxychloride. The reaction mixture was allowed to stand overnight at room temperature, was diluted with anhydrous ether, and the excess phosphorus oxychloride was decomposed by the dropwise addition of water. The water layer was removed and the ethereal solution was washed successively with fresh water, 10% sodium bicarbonate, and again with fresh water. The ethereal solution was dried over anhydrous potassium carbonate, filtered, and most of the solvent was evaporated. Crystallization was effected from ether–ethanol–water, furnishing 49 mg. (33%) of 6-methylcholesteryl acetate (IIIb), m.p. 112.5–113° (lit.[4] m.p. 115.5–116.5°).

B. By the Action of *p*-Toluenesulfonic Acid in Acetic Acid.—To a solution containing 6.794 g. (14.51 mmoles) of 6β-methylcholestan-3β,6α-diol monoacetate (IIb) dissolved in 370 ml. of acetic acid was added 503 mg. of *p*-toluenesulfonic acid monohydrate. The mixture was heated under reflux for 25 minutes, and then cooled to room temperature and diluted with water until crystallization ensued, yielding 5.694 g. (87.4%) of 6-methylcholesteryl acetate (IIIb), m.p. 112–113.75°. This material was saponified without further purification. A mixture melting point with the material obtained by dehydration with phosphorus oxychloride was not depressed.

6-Methylcholesterol (IIIa).—6-Methylcholesteryl acetate (IIIb) (5.394 g., 12.2 mmoles) was dissolved in 200 ml. of 95% aqueous ethanol containing 4.0 g. of potassium hydroxide. The reaction mixture was heated under reflux for 40 minutes and then diluted with water to crystallization. On cooling, the crystalline material was filtered, washed with *ca.* 30 ml. of 50% aqueous ethanol, and dried, yielding 4.444 g. (90.9%) of crude 6-methylcholesterol (IIIa), m.p. 144.5–145.25°. The analytical sample was prepared by repeated crystallization from ethanol–water, m.p. 144.5–145.25°, $[\alpha]^{30}D$ −46.4° (chloroform), $[\alpha]^{27}D$ −43.2° (9:1 dioxane–water) (lit.[4] m.p. 138.5–140.5°, $[\alpha]D$ −36.8° (dioxane); lit.[2] m.p. 134.5–135°).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.06. Found: C, 83.70; H, 12.28.

6-Methylcholesteryl *p*-Toluenesulfonate (IIIc).—A solution containing 4.082 g. (9.74 mmoles) of 6β-methylcholestan-3β,6α-diol (IIa) and 3.177 g. (16.7 mmoles) of *p*-toluenesulfonyl chloride in 25 ml. of anhydrous pyridine was allowed to stand at room temperature for 44 hours. A magnetic stirring bar was placed in the flask and to this reaction mixture (containing crystals of pyridine hydrochloride), cooled to 0°, was added dropwise 10.0 ml. of thionyl chloride with stirring and continued cooling. After the addition was complete (*ca.* 10 minutes) the reaction mixture was diluted with large quantities of anhydrous ether and excess thionyl chloride was decomposed by the dropwise addition of water. This water layer was removed and the ethereal solution was washed twice with fresh water, dried over potassium carbonate, and filtered.

The solution was concentrated to about 25 ml. *in vacuo*, acetone was added, and more solvent was removed *in vacuo*. On cooling to −80°, a white crystalline material separated and was filtered off. Repeated concentration of the mother liquor and subsequent cooling furnished a second and a third crop. These combined crops after drying weighed 4.686 g. (86.5%) and had m.p. 126.5–130.5° dec. The analytical sample was prepared by crystallization from pentane at −80° $[\alpha]^{27}D$ −43.5° (chloroform).

Anal. Calcd. for $C_{35}H_{54}SO_3$: C, 75.76; H, 9.81. Found: C, 76.40; H, 10.48.

Some preparations of this ester showed discoloration on standing at room temperature for two or three days. The decomposition appears to be autocatalytic. The melting points of the various preparations of this ester were erratic, some fairly pure samples decomposing before melting below 100°.

Acknowledgments.—This work was supported in part by a generous grant from the du Pont Co. The microanalyses were performed by Mrs. C. S. Yeh, and the nuclear magnetic resonance spectra were run by Mr. Ben Shoulders of the University of Illinois.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Optical Rotatory Dispersion Studies. XVI.[1] Synthesis and Conformation of Optically Active Octalones and Decalones[2]

BY CARL DJERASSI AND D. MARSHALL[3]

RECEIVED JANUARY 25, 1958

Collidine dehydrobromination of (−)-2-bromo-*trans*-9-methyl-3-decalone (IV) afforded (+)-Δ^1-*trans*-9-methyl-3-octalone (V) and (−)-Δ^4-9-methyl-3-octalone (VI), whose rotatory dispersion curves are similar to those of Δ^1-cholesten-3-one and Δ^4-cholesten-3-one, respectively. The dispersion curve of (−)-*cis*-9-methyl-3-decalone (VII), obtained by catalytic hydrogenation of (−)-Δ^4-9-methyl-3-octalone (VI), indicates that such *cis*-decalones and 3-keto-5β-steroids exist in the same conformation. The same statement also can be made about the conformations of *trans*-10-methyl-1-decalone (XI) and 4-keto-5α-steroids, such as cholestan-4-one (XV). The rotatory dispersion results indicate, however, that this does not appear to be the case with coprostan-4-one (XIV) and (−)-*cis*-10-methyl-1-decalone (X), the exclusive product of hydrogenation of (+)-Δ^8-10-methyl-1-octalone (VIII). The latter, in turn, was synthesized by an application of the "hetero-Δ^1-steroid rearrangement" from (−)-2-bromo-*trans*-9-methyl-3-decalone (IV). The conformational distortion produced by a 6,7-double bond or a 4,4-*gem*-dimethyl grouping is also illustrated by rotatory dispersion measurements of appropriate, optically active, bicyclic model compounds.

(1) Paper XV, C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

(2) Supported by a research grant (No. CY-2919), from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) Postdoctorate research fellow, 1956–1957.