[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Solvolysis of 4,4-Dimethylcholesteryl-*p*-toluenesulfonate. II[1]

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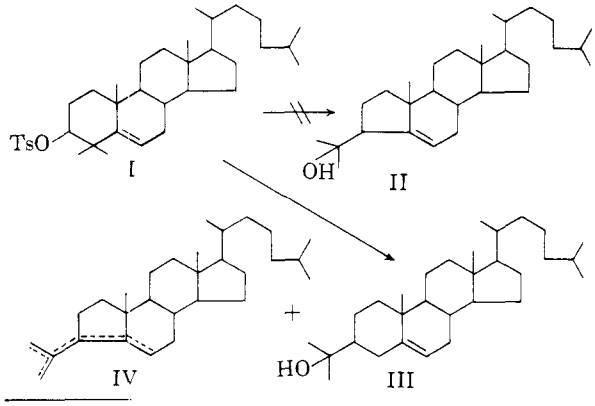
We have studied the solvolysis of 4,4-dimethylcholesteryl-*p*-toluenesulfonate (I) under conditions which favor the formation of a 3,5-cyclosterol ("*i*-sterol"). After completion of our investigation, another group of workers reported results on this problem.[2] These workers reached different conclusions concerning the structures of the products of this solvolysis. Their results are discussed and additional data obtained by us are here presented.

A general reaction which 3β-hydroxy-Δ⁵-sterols undergo is solvolysis *via* an intermediary homoallylic-type carbonium ion to yield a 3,5-cyclosterol as the product of kinetic control.[3] If, however, such a system be saturated and possess 3β-hydroxy,4,4-dimethyl substituents, as in the case of certain triterpenes, then rearrangement takes place with ring contraction to yield an A-nor-product.[4]

Therefore, it appeared to be of interest to study the solvolysis of compound I, which contains both a Δ⁵ double bond, and 4,4-dimethyl substituents since in such a molecule either or both of these reactions can conceivably take place, namely: formation of 4,4-dimethyl - 3,5 - cyclocholestan-6β-ol (II) or ring contraction to yield 3-(2-hydroxy-2-propyl)-A-norcholest-5-ene (III).

We have previously reported[1] that the solvolysis of 4,4-dimethylcholesteryl-*p*-toluenesulfonate (I) in 60% aqueous acetone in the presence of potassium acetate yielded 70% of a mixture composed of isomeric, conjugated dienes (IV), 20% 3-(2-hydroxy-2-propyl)-A-norcholest-5-ene (III) and 7% 4,4-dimethylcholesterol. No 4,4-dimethyl-3,5-cyclocholestan-6β-ol (II) was found.



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

(3) E. S. Wallis, E. Fernholz, and F. T. Gephardt, *J. Am. Chem. Soc.*, **59**, 137 (1937); H. H. Hafez, G. Halsey, and E. S. Wallis, *Science*, **110**, 474 (1949); S. Winstein and R. Adams, *J. Am. Chem. Soc.*, **70**, 838 (1948).

(4) W. Klyne, *Progress in Stereochemistry*, Butterworth's, London, 1954, Vol. 1, p. 70.

(5) We wish to thank LeRoy Johnson, Varian Associates, Palo Alto, Calif., for determining and interpreting the n.m.r. curve of this compound.

Recently there has appeared a paper by Y. M. Y. Haddad and G. H. R. Summers which is an account of their investigation of this reaction.[2]

Under the same solvolytic conditions as our experiment these investigators obtained the same products as reported by us. In contrast to our structural assignment, however, they concluded that the isomeric alcohol which we identified as 3-(2-hydroxy-2-propyl)-A-norcholest-5-ene (III) [m.p. 125–126°, $[\alpha]_D$ −24.7 (c, 0.8)] was an *i*-sterol (II).

They based their assignment of structure on the following data: (a) the method of preparation, (b) the hindered nature of the hydroxyl group, and (c) oxidation in a very small yield to a supposed *i*-ketone whose structural assignment was based on infrared absorption and microanalysis.

On the other hand, there are data in their paper which allow a different interpretation and which we believe can best be explained in terms of our structural assignment (III) which postulates a tertiary alcohol; namely (a) failure to acetylate, epimerize, and oxidize under the usual conditions for these reactions; (b) failure to undergo acid-catalyzed rearrangement to the normal alcohol, a property characteristic of 3,5-cyclosteroids; and (c) the sign of the rotatory power of the compound. All these latter observations we also made.

In addition, we reported certain other results on the isomeric laevorotatory alcohol in question: (a) the presence of a double bond as shown by bromine addition, decolorization of potassium permanganate solution, and a positive test with tetranitromethane; (b) oxidation to A-norcholest-5-en-3-one, identical with an authentic sample; and (c) dehydration to the conjugated diene, 3-isopropylidine-A-norcholest-5-ene (V). All these facts in our opinion were best explained on the assignment of a tertiary alcohol structure[1] for the compound of m.p. 125–126°.

In this paper we now wish to report further results obtained in our studies of this alcohol which we believe clearly disprove the 3,5-cyclosterol structure proposed by Haddad and Summers.[2]

The nuclear magnetic resonance spectrum[5] of III, measured at 60 m.c. with deuterochloroform as the solvent and tetramethylsilane as the internal standard, shows a signal at 333 c.p.s., a position characteristic of a proton on a doubly bonded

carbon. This n.m.r. result is incompatible with structure (II). In cholesterol the C_{18} peak is seen at 43 c.p.s. and C_{19} at 63 c.p.s. In the spectrum of III these two signals appear at 41 and 54 c.p.s., respectively. With the five-membered A-ring the two angular methyl groups are more nearly equivalent and so the two peaks are brought closer together.

Ozonolysis of compound III yields an amorphous product which possesses strong absorption in the infrared at 5.75–5.85μ, a fact in agreement only with our proposed structure, since it has been shown that the geminal dimethylcyclopropyl group[6] is unaffected by ozone.

Upon treatment of III with excess perbenzoic acid the compound reacts with an equivalent amount of the peracid as shown by titration to yield the epoxide 3-(2-hydroxy-2-propyl)-A-norcholestan-5.6-oxide (VI) m.p. 119–121°. The stability of the geminal dimethylcyclopropyl group to perbenzoic acid has been amply demonstrated[7] and so again a structure such as II would be unchanged when treated with this reagent.

In conclusion we would like to report a further observation on the work of Haddad and Summers.[2] As stated earlier in this paper, about 70% of the total product from the solvolysis of I is a mixture of dienic material. Haddad and Summers report this as a pure compound, 3-isopropylidene-A-norcholest-5-ene (m.p. 85°) $[\alpha]_D^{22}$ −65.7 (*c*, 1.4), $\lambda_{max.}$ 241mμ; log ϵ 4.22. This is incorrect; it is a mixture. We have prepared this compound (V) in a pure state by phosphorus oxychloride-pyridine dehydration of III. The compound melts at 102–104° $[\alpha]_D^{22}$ −168.4; λ_{max} 249 mμ, log ϵ 4.14. On the basis of empirical rules for predicting the position of the ultraviolet spectrum it is evident that the value of 241 mμ is too low for V, if one considers the degree of substitution and exocyclic arrangement of the conjugated double bonds.[8,9]

EXPERIMENTAL[10]

Solvolysis of 4,4-dimethylcholesteryl-p-toluenesulfonate (I). A solution of 2.58 g. of ester, 2.83 g. of potassium acetate, and 50 ml. of water in 75 ml. of acetone was kept at reflux for 15 hr. Then most of the acetone was removed under reduced pressure. The remaining aqueous portion was extracted with ether. The combined extracts were dried and concentrated *in vacuo*. The residual oil was dried further under high vacuum, resulting in a thick, clear, semiviscous gum, 1.92 g. This product was dissolved in a small volume of ether and absorbed on a column of 100 g. of neutral alumina. Elution with 200 ml. of pentane yielded 1.37 g. of a clear, viscous oil. Further elution with 8:2 ether chloroform and 1:1 ether chloroform yielded 540 mg. of crystalline material. The 1.37 g. of oil was crystallized from acetone at −78° to yield 1.0 g., m.p. 49–60°. This material was chromatographed on 30 g. neutral alumina, and fractional elution with *n*-pentane gave diene IV, 720 mg., m.p. 78–80°, $[\alpha]_D^{22}$ −126.6° (*c*, 0.73), $\lambda_{max}^{CCl_4}$6. 02μ, λ_{max}^{EtOH} 242 mμ, ϵ 13,990, sh. 238 mμ, ϵ 13,200, 250 mμ, ϵ 10,560. The analytical sample, prepared by repeated recrystallization from acetone, had m.p. 84–86°.

Anal. Calcd. for $C_{29}H_{48}$: C, 87.80; H, 12.20. Found: C, 87.59; H, 12.50.

The 540 mg. of crystalline material was rechromatographed on 20 g. acid washed alumina. Elution with 1:1 pentane ether gave III, 300 mg., m.p. 120–122°. The analytical sample prepared by recrystallization from acetone had m.p. 125–126°, $[\alpha]_D^{22}$ −21.90° (*c*, 2).

Anal. Calcd. for $C_{29}H_{50}O$: C, 84.00; H, 12.15. Found: C, 84.26; H, 12.45.

Further elution with pure ether gave 100 mg. of material m.p. 142–144° which was identified as 4,4-dimethylcholesterol (IV) by a mixed melting point determination and infrared absorption comparison with authentic IV.

Perbenzoic acid titration of III. The samples were dissolved in chloroform and a solution of perbenzoic acid in chloroform (7.5 mg./ml.) was added. After being stored overnight at 2°, an aqueous solution of sodium iodide and 3 drops of acetic acid were added. The liberated iodine was titrated with 0.1212*N* sodium thiosulfate: (a) 45.5 mg. (0.109 mml.) III requires 15.07 mg. of perbenzoic acid, 30 mg. was added, and 1.83 ml. of 0.1212*N* sodium thiosulfate was required to titrate the excess iodine; (b) 101.5 mg. (0.245 mml.) requires 33.8 mg. of perbenzoic acid, 52.5 mg. was added, and 2.30 ml. of 0.1212*N* sodium thiosulfate was required to titrate the excess; (c) 93.5 mg. (0.226 mml.) III requires 31.4 mg. of perbenzoic acid, 45.0 mg. was added, and 1.66 ml. of 0.1212*N* sodium thiosulfate was needed to titrate the excess; (d) 46.1 mg. (0.119 mml.) of cholesterol requires 16.45 mg. of perbenzoic acid, 30.0 mg. was added, and 1.63 ml. of 0.1212*N* sodium thiosulfate was used to titrate the excess iodine. All these results indicate the presence of *one* double bond in the molecule.

3-(2-Hydroxy-2-propyl)-A-norcholestan-5,6-oxide (VI). To a solution of 200 mg. of III was added 12 ml. of a solution of perbenzoic acid in chloroform which contained 7.5 mg. perbenzoic acid per ml. The solution was stoppered and stored overnight at 2°. Water was added followed by extraction with chloroform. The chloroform solution was washed with a saturated solution of sodium bicarbonate and water, dried, and concentrated *in vacuo*. The crude product crystallized upon trituration with acetone. It was recrystallized from acetone to yield 150 mg. m.p. 119–121°, $[\alpha]_D^{23}$ −14° (*c*, 2).

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.85; H, 11.79.

Ozonolysis of III. One hundred mg. of III was dissolved in 5 ml. of chloroform. At 0° ozone was passed through the solution for 0.5 hr. Water was added and the mixture was stirred for 0.5 hr. The chloroform layer was separated, dried, and concentrated *in vacuo*, yielding a gum which failed to crystallize from the usual solvents. $\lambda_{max}^{CCl_4}$ broad 5.75–5.85μ.

3-Isopropylidene-A-norcholest-5-ene (V). To a solution of 200 mg. of II dissolved in 2 ml. of pyridine, 2 ml. of phosphorus oxychloride was added. After heating at reflux for

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(8) R. B. Woodward, *J. Am. Chem. Soc.*, **64**, 72 (1942).

(9) Compare abietic acid and neoabietic acid, G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 339 (1948).

(10) Melting points were taken on a Kofler block and are uncorrected. Rotations were taken using chloroform as the solvent. The microanalyses were performed by George Robertson, Florham Park, N. J. Tetramethylsilane was used as the internal standard in the n.m.r. spectrum determination and deuterochloroform was the solvent.

1 hr., the reaction mixture was cooled and ice water cautiously added. The reaction mixture was extracted with ether and the ethereal extracts were washed with cold dilute hydrochloric acid and a saturated solution of sodium bicarbonate, dried, and concentrated *in vacuo*. The resulting crystalline product, 180 mg., was recrystallized from acetone to yield 135 mg. of V, m.p. 102–104°, $[\alpha]_D^{22}$ −168 (*c*, 2), λ_{max}^{EtOH} 249 mμ, log ε 4.22.

Anal. Calcd. for $C_{29}H_{48}$: C, 87.80; H, 12.20. Found: C, 88.10; H, 12.33.

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Labor-saving Procedures for Calculating Wave Functions for Molecules with Axes of Symmetry

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Detailed procedures are given for calculating the first approximation LCAO-MO energies and wave functions for the π-electrons of molecules with *n* conjugated atoms and a two- or k-fold axis of rotation.

Organic chemists make increasing use of approximate calculations of resonance energy, charge distribution, bond order, force constant, free valence and localization energy (Dewar reactivity number) in correlating and predicting structures and reactivities of unsaturated systems.[1] General procedures have been described for evaluating these quantities for the π-electrons of any molecule with *n* conjugated atoms using the first-approximation LCAO-MO method.[2] These generally call for solution of an $n \times n$ determinant. When *n* is large, as in triphenylmethyl, the work involved becomes prohibitive unless a digital computer is employed. However, the work can be appreciably reduced whenever the molecule has a two- or *k*-fold axis of rotation by replacing the $n \times n$ determinant by two or more smaller determinants. This can be done by choosing trial wave functions belonging to families of different basic symmetry (Γ-types) so that no two from different families will have any resonance integrals (*i.e.*, off-diagonal elements between them in a secular determinant involving them as trial functions). Then only trial functions of the same family can interact with one another. Rules for choosing trial functions belonging to different families are given below for several kinds of molecular symmetry. Benzene will be used as an illustration in each section because it has each of these kinds of symmetry. Although the derived molecular wave functions may depend on the approach, the energies, charges, bond orders, and free valences do not. These useful procedures may be familiar or obvious to many physical chemists, but the authors know of no single source where one may find them described concisely for the cases of interest to organic chemists.

Two-fold axis. Ethylene, propene, butadiene, benzene, phenanthrene, pentadienyl, and benzyl radicals all have a two-fold axis for their π-electrons. Number all conjugated atoms of the molecule and tabulate them in a vertical column. Beside each in an adjacent column write the number of the atom it becomes after a 180° rotation about the two-fold axis. For minimum size determinants, choose the axis so that as many numbers change as possible. Now use the character table

Determinant	E	C_2^z	Family
D_1	1	1	Γ_1
D_2	1	−1	Γ_2

to generate trial wave functions ψ_1, ψ_2... for use in each determinant D by taking "dot products" of the E, C_2^z characters by the atomic wave functions corresponding to the pairs of numbers thus tabulated (see first example, which illustrates this process). Normalize each of these trial functions by dividing through by the sum of the squares of the coefficients. For each determinant D

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