The Acid-Catalyzed Rearrangement of Enol Ester Epoxides

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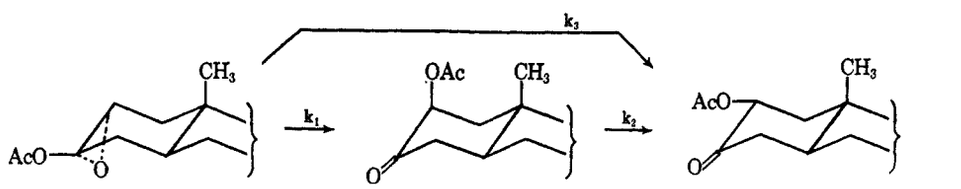
The acid-catalyzed rearrangement of enol ester epoxides has been shown to be intramolecular, to involve acetate migration with retention of configuration, and to be initially first order in acid and first order in epoxy-ester. The thermal and acid-catalyzed rearrangements of enol ester epoxides are shown to proceed through quite different mechanisms, in sharp contrast to mechanisms previously proposed for this reaction. A detailed study reveals that 3β-acetoxy-2,3-α-epoxycholestane (I) will rearrange in acid to 2α-acetoxycholestan-3-one (III) a thousand times faster than 2β-acetoxycholestan-3-one (II) will epimerize to the same 2α-acetoxy ketone (III) (*p*-toluenesulfonic acid in chloroform at 25°).

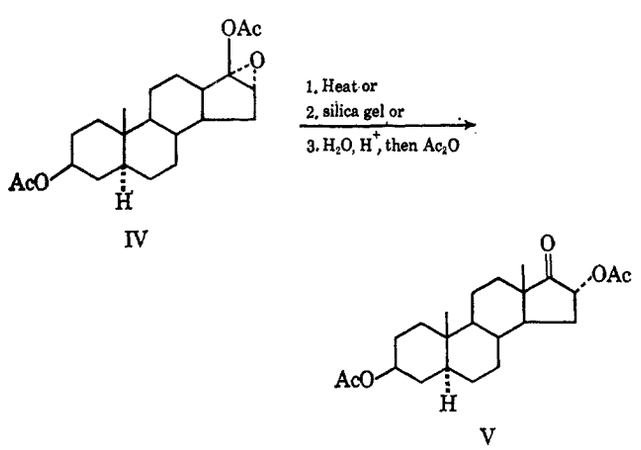
Enol ester epoxides rearrange on heating to α-acetoxy ketones. The rearrangement occurs in high yield with clean inversion of configuration. For example when I is heated above its melting point for a few minutes it gives the β-acetoxy ketone (II) in 85% yield.[2] Acid can then be used to convert II to the more stable equatorial acetoxy ketone (III); heat alone will not effect this epimerization.[2] This was the first clear evidence for the stereospecificity of the thermal rearrangement of an epoxy acetate. Previously it had been shown that the epoxy acetate (IV) rearranges to V by the action of heat, by chromatography on silica gel, and by acid hydrolysis followed by reacetylation.[3]



3β-acetoxy-2,3α-epoxycholestane (I)
[α]²⁵D +16.5° (1.60 chloroform)
mp 133–134.5°
silica gel tlc R_f 0.47

2β-acetoxycholestan-3-one (II)
[α]²⁵D +86.9° (1.79 chloroform)
mp 145–146°
R_f 0.27

2α-acetoxycholestan-3-one (III)
[α]²⁵D +51.6° (1.67 chloroform)
mp 124.7–125.2°
R_f 0.37



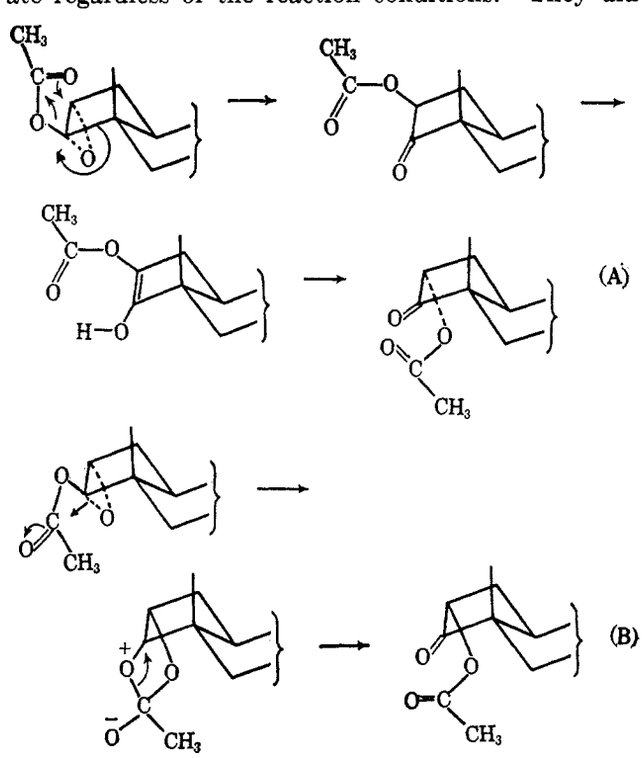
IV

V

Two possible mechanisms were proposed[3] to rationalize the conversion of IV to V. The first of these (A), proposed by R. B. Woodward at a Gordon Conference and quoted by Leeds, *et al.*, assumes that the acetate migrates with inversion to give the 16β orientation of a hydroxyl or an acetoxyl group, which, being unfavored sterically, will rearrange to the more stable 16α configuration under mild enolizing conditions.[4]

An alternative mechanism (B) involves opening of the epoxide ring to an ionic intermediate which gives the observed α-acetoxy ketone directly.

Leeds, Fukushima, and Gallagher[3] made the tacit assumption that either mechanism A or B might operate regardless of the reaction conditions. They did not consider the possibility that different mechanisms might operate for *thermal* and *acid-catalyzed* rearrange-



(1) (a) National Science Foundation Undergraduate Research Participant, 1963–1964, 1964–1965; (b) Petroleum Research Fund Scholar, 1965.

(2) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961); *J. Am. Chem. Soc.*, **83**, 4623 (1961).

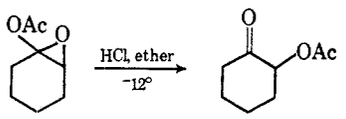
(3) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *ibid.*, **76**, 2943 (1954). See also A. H. Soloway, W. J. Considine, D. K. Fukushima and T. F. Gallagher, *ibid.*, 2941 (1954).

(4) *Cf.* W. S. Johnson, B. Gastambide, and R. Pappo [*ibid.*, **79**, 1991 (1957)] who have shown that 3β,16β-diacetoxyandrostan-17-one will not epimerize to the 16α compound on treatment with silica gel.

ments of epoxy acetates. In the present work we will show that epoxy acetates follow quite different paths to products depending on conditions. Although *heat* will convert the ring A epoxy acetate I to the axial acetoxy ketone (II), *acid* converts the apoxy acetate I *directly* to the equatorial acetoxy ketone (III) without the intervention of the axial acetoxy ketone (II).

Results and Discussion

Treatment of the monocyclic epoxy acetate (VI) with gaseous hydrogen chloride in ether at −12° causes quantitative rearrangement to 2-acetoxycyclohexanone (VII). No trace of the product of nucleo-



VI VII

philic attack, 2-chlorocyclohexanone, was detected in the infrared spectrum of the crude rearranged material. This experiment does not, of course, allow any conclusion to be drawn concerning the intra- or intermolecularity of the reaction, the stereochemistry of the rearrangement, or even the positional isomerism of the product. It has been shown by Shine and coworkers[5] that the *thermal* rearrangement of epoxy acetates of this type proceeds with acetate migration and is intramolecular. This they demonstrated by thermally rearranging 1-acetoxy-1,2-epoxy-4-methylcyclohexane in the presence of 1-propionoxy-1,2-epoxycyclohexane to give the corresponding 1-keto esters with no cross products.

In order to study the *acid-catalyzed* rearrangement of epoxy acetates in some detail we turned our attention to the steroid ring A compound I which we had previously prepared and characterized.[2] Treatment of the epoxy acetate I with 48% hydrobromic acid in chloroform for 5 min with agitation, with gaseous hydrogen chloride in benzene overnight, with acetic acid in chloroform overnight, or with *p*-toluenesulfonic acid in chloroform overnight gave products shown by their infrared spectra to be identical with each other and quite different from the epoxy acetate starting material. The spectra were virtually identical with the spectrum of 2α-acetoxycholestan-3-one (III) and quite different, especially in the highly characteristic 9–10-μ range, from three other possible rearrangement products of which we had authentic samples: 2β-acetoxycholestan-3-one (II) and 3α- and 3β-acetoxycholestan-2-one.[6]

The three isomeric compounds (I, II, and III) differ markedly in many of their physical properties in addition to their infrared spectra (see above). In an initial study we chose to follow the conversion of I to III by thin layer chromatography (tlc) on silica gel. Since heating I above its melting point gives II in high yield[2] we thought it might be possible to detect the presence of II as an intermediate in the acid-catalyzed conversion of I to III. Such did not prove to be the case. Rearrangement of a 0.1 *M* solution of the epoxy acetate I in a chloroform solution 0.002 *M* in *p*-toluenesulfonic acid proceeded slowly to give entirely III after 24 hr. No spot corresponding to II could be observed during the reaction. This was confirmed by following the optical rotation as a function of time. The specific rotation rose steadily from an initial value near 16.5° and stopped at 52° without ever going above 52° as it might have if an appreciable concentration of II ($[\alpha]_D$ +86.9°) were present. This behavior can be rationalized in at least two ways: a slow, rate-determining rearrangement of I to II and then a fast epimerization of II to III, or direct rearrangement of I to III without the intervention of II. With a sample of the pure axial keto acetate II in hand we were in a position to distinguish between these two alternatives.

To our surprise, acid treatment of a chloroform solution of the sterically hindered axial keto acetate (II) under exactly the same conditions as were used to rearrange I to III caused no significant change in the specific rotation over a 21-hr period. After washing out the acid, the infrared spectrum of the solution showed that II was unchanged. Only by greatly increasing the acid concentration could the rearrangement of II to III be made to proceed at a measurable rate.

Before making a more careful study of the kinetics of this rearrangement we sought to show that the rearrangement was intramolecular and that the product was primarily the 2α-acetoxy ketone (III). In parallel experiments the epoxy acetate (I) in chloroform was treated with a 10 *M* excess of acetic acid and separately with a 10 *M* excess of propionic acid. After 34 hr the observed rotations become constant and the reaction mixtures were worked up. The infrared spectra of the products were shown to be identical. Even more convincing was the observation that running the *p*-toluenesulfonic acid catalyzed rearrangement in the presence of C^{14}-labeled acetic acid gave, within the experimental errors of measurement, no incorporation of activity in the product. In all the rearrangements that proceeded to completion the infrared spectra of the products were virtually identical with the spectrum of an authentic sample of 2α-acetoxycholestan-3-one. It was difficult to obtain III having a sharp melting point by direct crystallization of the reaction mixture.[7] Chromatography of the reaction mixture on alumina, however, gave 77% of crystalline material as the only product, which on recrystallization had a melting point and mixture melting point identical with that of III. There is the possibility that the equatorial keto acetate (III) exists in equilibrium with a very small amount of the axial keto acetate (II), causing melting point depression. The ultraviolet spectrum of the crude rearranged product (after work-up) showed a shoulder at 225 mμ and a very small peak at 255 mμ indicating very slight contamination (less than 1%) by a tosylate ester.

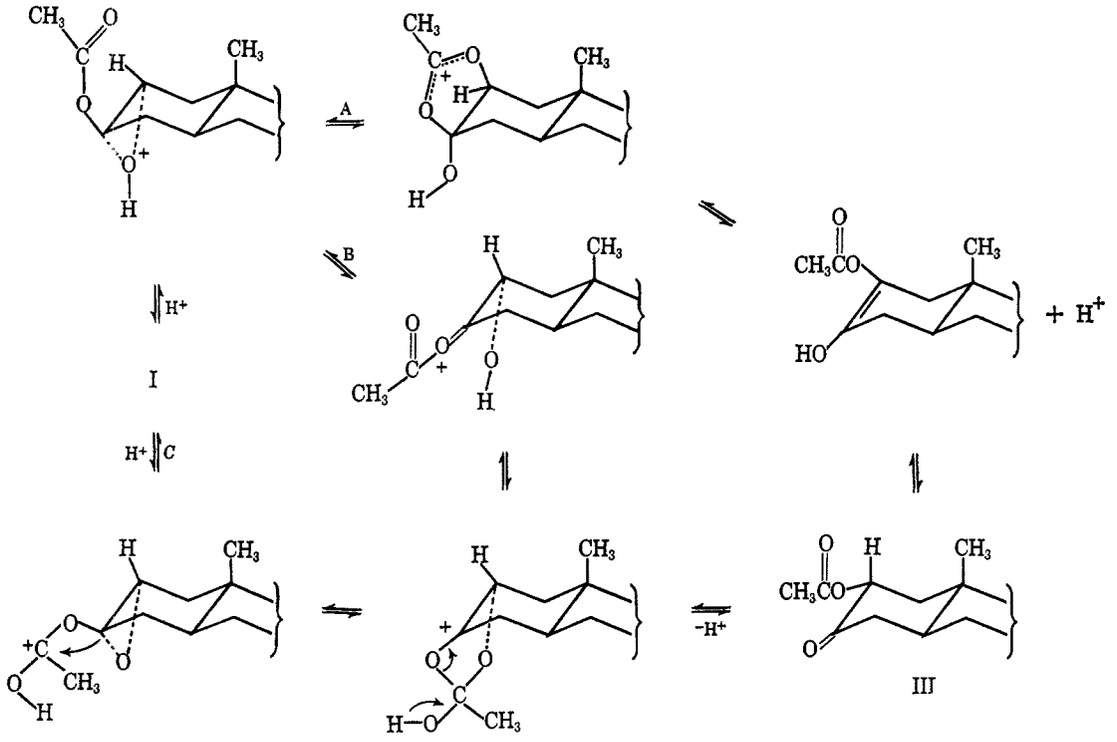
Having shown that the acid-catalyzed rearrange-

(5) A. L. Draper, W. J. Heilman, W. E. Schaefer, H. J. Shine, and J. N. Shoolery, *J. Org. Chem.*, **27**, 2727 (1962).

(6) Similarly it has recently been reported [James R. Rhone and Max N. Huffman, *Tetrahedron Letters*, 1395 (1965)] that 16α,17α-epoxyestra-1,3,5(10)-triene-3,16β-diol diacetate rearranges quantitatively to 16-keto-estra-1,3,5(10)-triene-3,17α-diol diacetate on treatment with perchloric acid in acetic acid. This involves the same type of change in stereochemistry as observed in the present work.

(7) In our previous work on these isomeric keto acetates[2] it was noted that very slight contamination of one isomer with another resulted in very great melting point depressions.

SCHEME I



ment of the epoxy acetate (I) gives only the keto acetate (III) by an intramolecular pathway, we turned our attention to the kinetics of the rearrangement. The course of the reaction was easily followed by observing the change in specific rotation as a function of time. This reaction, in which the acid concentration remains constant, follows pseudo-first-order kinetics.[8] From a plot of the specific rotation *vs.* time a pseudo-first-order rate constant is obtained, which on division by the acid concentration gives the second-order rate constant. The rate constant of the *p*-toluenesulfonic acid catalyzed conversion of I to III (chloroform at 25°) was found to be *ca.* 20 l. mole^{-1} min^{-1}. The rate constant of the epimerization of the axial keto acetate (II) to the equatorial keto acetate (III) under the same conditions was found to be *ca.* 0.02 l. mole^{-1} min^{-1}. This 1000-fold difference in the rates of these two reactions indicates quite clearly that the epoxy acetate (I) must rearrange to the equatorial keto acetate (III) without going through the axial keto acetate (II), in sharp contrast to the thermal rearrangement of the epoxy acetate (I).

A variety of mechanisms can be proposed for this acid-catalyzed rearrangement that differ primarily in the order of bond breaking and bond making (Scheme I). Path A could be distinguished from paths B and C by O^{18} labeling of the epoxide oxygen. If the reaction followed path A the label would be incorporated into the carbonyl of the product whereas if it followed paths B or C the label would reside in the acetate group of the product.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus at a heating rate of 2°/min and are uncorrected. Infrared spectra were run on Perkin-Elmer 137 and Beckman IR-4 spectrometers as 10% solutions in chloroform. Ultraviolet spectra were run on a Perkin-Elmer 205 spectrometer. Optical rotations were determined with a Perkin-Elmer 141 photoelectric polarimeter and a Rudolph Model 70 polarimeter employing the D line of sodium. Benzene and petroleum ether (bp 46–85°) were distilled before use.

1-Acetoxy-1,2-epoxycyclohexane (7-Oxabicyclo[4.1.0]heptanol Acetate) (VI).—In a $^{14}/_{20}$ round-bottom flask equipped with thermometer, condenser, and dropping funnel was placed 13.9 g (0.1 mole) of 1-acetoxycyclohexene [bp 74–76° (16 mm)] in 25 ml of chloroform. The flask and contents were cooled to 10° and a solution of 21.9 g (0.11 mole) of 85% *m*-chloroperbenzoic acid (FMC Corp.) in 50 ml of chloroform was added dropwise over 25 min. At intervals 1-ml aliquots were taken and weighed; the iodine liberated on addition of 10% potassium iodide solution was titrated with 0.1 *N* sodium thiosulfate to a starch indicator end point. After 35 min the mixture was cooled in ice and filtered to remove *m*-chlorobenzoic acid. An aliquot showed 0.5% per acid remaining. The chloroform solution was washed with 10% sodium sulfite until neutral to starch–iodide paper, then with 5% sodium bicarbonate until neutral to litmus, and with one portion of saturated sodium chloride solution. The chloroform solution was stored over anhydrous sodium sulfate at −12°. The solvent was removed on a rotary evaporator below room temperature and the residue distilled through a short Vigreaux column taking great care to avoid overheating. This gave 10.4 g (66%) of the epoxy acetate: bp 35.5–36.5° (0.2 mm); n^{25}D 1.4489; infrared λ_{max} 5.78, 7.38, 8.3 (br), and 8.66 μ. Reported by Shine and Hunt[9] is a 55% yield of material, bp 44–48° (2 mm), n^{25}D 1.4475.

2-Acetoxycyclohexanone (VII).—This compound was prepared by heating the epoxy acetate (VI) at 100° for a few minutes. The crude crystalline material recrystallized from petroleum ether had mp 36–37°; infrared λ_{max} 5.79, 7.29, 8.3 (br), 9.21, and 9.34 μ. Reported by Shine and Hunt[10] is mp 34–35°.

Hydrogen Chloride Treatment of 1-Acetoxy-1,2-epoxycyclohexane (VI).—In a flask fitted with a magnetic stirrer, thermometer, and gas inlet tube was placed 3 g (0.019 mole) of 1-acetoxy-1,2-epoxycyclohexane (VI) in 25 ml of ether. The solution was cooled to −12° and stirred as 1.7 g of gaseous hydrogen chloride was condensed. The reaction mixture was kept at −12° overnight, then washed quickly with one 50-ml portion of cold water, two 5-ml portions of 5% sodium bicarbonate solution, and one 5-ml portion of saturated sodium chloride solution. After drying over anhydrous sodium sulfate

(8) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 559.

(9) H. J. Shine and G. E. Hunt, *J. Am. Chem. Soc.*, **80**, 2434 (1958).

the solvent was removed at reduced pressure at room temperature and below. The residual yellow oil spontaneously crystallized. An infrared spectrum of the crude product indicated it was almost entirely 2-acetoxycyclohexanone (VII). No 2-chlorocyclohexanone could be detected in the crude product (absence of bands at 5.81, 6.92, 7.02, 7.71, and 8.95 μ seen in an authentic sample prepared according to a procedure in "Organic Syntheses"[10]). On recrystallization from petroleum ether the product had mp 35–36°, undepressed on admixture with an authentic sample of 2-acetoxycyclohexanone.

Acid-Catalyzed Rearrangement of 3β-Acetoxy-2,3α-epoxycholestane (I).—The steroid epoxyacetate (I) prepared as described before[4a] had mp 132.5–134°, $[\alpha]^{25}D$ 16.5° (1.60 chloroform). In preliminary experiments it was shown that the rotation and infrared spectrum of a 0.1 *M* solution of this material in Fisher AR grade chloroform did not change over a 48-hr period when stored at room temperature; this chloroform was employed for all subsequent experiments. A sample of pure white Fisher reagent grade *p*-toluenesulfonic acid monohydrate required 99.98% of the theoretical amount of 0.100 *N* sodium hydroxide solution for neutralization to a phenolphthalein end point and was employed without further purification.

A. Intramolecularity of the Rearrangement. 1.—The optical rotation of a solution of 247 mg (0.55 mmole) of the epoxy acetate (I) and 0.33 ml (5.5 mmoles) of glacial acetic acid in 4.67 ml of chloroform was followed for 34 hr. In a parallel experiment 247 mg (0.55 mmole) of I and 0.41 ml (5.5 mmoles) of propionic acid were dissolved in 4.59 ml of chloroform. The observed rotations of both solutions increased over a 24-hr period and then remained constant. Each solution was diluted with ether, washed with sodium bicarbonate solution, water, and saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The infrared spectra of the solid residues obtained after removal of the solvent were identical in all respects and were virtually identical with the spectrum of an authentic sample of 2α-acetoxycholestan-3-one (key bands at 9.21 and 9.60 μ).

2.—A few milligrams of $C^{14}H_3COONa$ was dissolved in 0.3186 g (5.306 mmoles) of acetic acid and made up to 25 ml (36.5622 g) with chloroform. Aliquots of 0.5 ml (0.7336 g) were neutralized with potassium hydroxide in methanol on counting planchets and evaporated to dryness. After correcting for the background these samples showed an activity of 260 cpm. In a 2.03-ml volumetric flask was placed 74.8 mg (1.68×10^{-4} mole) of the epoxy acetate (I) and 0.5 ml of the active chloroform solution of acetic acid. The flask was made up to volume with a 0.0247 *M* solution of *p*-toluenesulfonic acid in chloroform. After the rearrangement was complete (2 hr) the mixture was diluted with ether, washed with sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. The ether–chloroform solutions were distributed over six planchets, evaporated, weighed (recovery quantitative), and counted. After correction for background the planchets showed between 0 and 1 cpm. It was concluded that a negligible amount of active acetate was incorporated into the steroid. Radiation was detected with a thin window (1.4 mg/cm²) geiger tube made by Tracerlab, Inc. It was set at 0.25 sensitivity, 1300 v and 1000 cpm.

B. Product of the Rearrangement.—A solution of 241 mg of the epoxy acetate (I) and 4.9 mg of *p*-toluenesulfonic acid in 5 ml of chloroform was sampled periodically for tlc. Eastman Chromagram sheet type K 301R (silica gel) was employed with benzene as the eluent and iodine as the developer. The spot at R_f 0.47 (I) gradually was replaced by one at R_f 0.37 (III). No spot at R_f 0.27 corresponding to II was observed. The spot due to *p*-toluenesulfonic acid did not move from the origin.

Rearranged material (43.9 mg) after work-up in the usual manner was chromatographed on 2.5 g of Florisil. The material eluted by 50–70% benzene in petroleum ether (33.8 mg, 77%) was combined and recrystallized from ethanol to give plates, mp 123–124° undepressed on admixture with authentic 2α-acetoxycholestan-3-one. Crude rearranged material, after work-up, exhibited a shoulder at 225 mμ and a peak at 225 mμ in the ultraviolet spectrum (ethanol solvent). If this were tosylate ester, it would represent about 1% of the total crude rearranged product.

C. Kinetics of the Rearrangement.—Kinetic studies were made over a tenfold range of acid concentrations (0.4–3.4 mg/ml of reaction mixture) and a tenfold range of substrate concentrations. In a typical kinetic run 0.3846 g of the epoxy acetate (I), mp 132.5–134°; was dissolved in 5.00 ml of chloroform at 25.5° that was 0.00515 *M* in *p*-toluenesulfonic acid monohydrate. The solution was mixed thoroughly and poured into a 1-dm polarimeter tube thermostatted at 25.5 ± 0.2°. Readings of the rotation were taken every 15 sec (on a Perkin-Elmer 141 photoelectric polarimeter) for 1 hr at which time the rotation ceased changing. The pseudo-first-order rate constant for each point was calculated (by computer) according to

$$k_0 = \frac{1}{t} \ln \frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty}$$

where α_0 is the specific rotation of the epoxy acetate (V) (16.5°), α_t is the rotation at time t, and α_∞ is the specific rotation after the rearrangement is complete (53.6°). The specific rotation of 2α-acetoxycholestan-3-one is reported[2] to be 51.6° (1.67 chloroform). Typically k_0 remained constant during the first several half-lives of the reaction although it increased to approximately twice its initial value by the end of the reaction.

The initial rate law assumed for the rearrangement is $-$d[epoxy acetate (V)]/dt = k_3[epoxy acetate (V)][TsOH] where [TsOH] is the total formal concentration of *p*-toluenesulfonic acid. For constant acid concentration this reduces to $-$d[epoxy acetate (V)]/dt = k_0[epoxy acetate (V)], where k_0 = k_3[TsOH].

The initial rate constant for the rearrangement of the epoxy acetate (I) to the α-acetoxy ketone (III) is *ca.* 20 l. mole^{-1} min^{-1}. The initial rate constant for the corresponding rearrangement of the β-acetoxy ketone (II) was found to be *ca.* 0.02 l. mole^{-1} min^{-1}. (It was necessary to increase the acid concentration by at least a factor of 50 to cause the latter reaction to occur in a reasonable length of time.) The products from both rearrangements were shown to be identical in all respects by comparison of their infrared spectra. Because of poor temperature control and some scatter in the data obtained from the Rudolph Model 70 polarimeter (on which most of the runs were made) the rates obtained are probably accurate to only one significant figure.

Registry No.—I, 7459-00-9; II, 14362-45-9; III, 14161-45-6; VI, 14161-46-7.

Acknowledgments.—We are indebted to Professors Jerrold Meinwald and William S. Johnson for suggestions regarding the mechanisms proposed. We would also like to acknowledge the financial support of the Petroleum Research Fund and the U. S. Public Health Service (GM-10224). We are grateful for the use of the Perkin-Elmer 141 polarimeter at Smith College and for the use (*via* time sharing) of the GE-235 computer at Dartmouth College.

(10) M. S. Newman, M. D. Farbman, and H. Hipsher, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y. 1955, p 188.