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MOLECULAR REARRANGEMENTS IN THE STEROLS. VIII. THE KINETICS OF THE ACID REARRANGEMENT OF 3,5-CYCLOCHOLESTAN-6β-OL (*EPI-I*-CHOLESTEROL)

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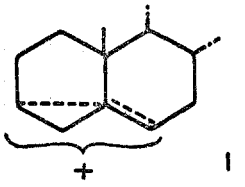
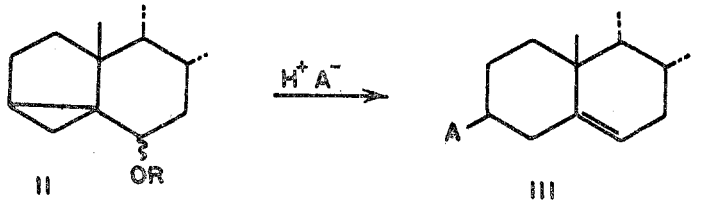
The failure of 3,5-cyclosterols to form stable *p*-toluenesulfonates (1) eliminated the possibility of studying the rate of the acid rearrangement, analogous to the reverse reaction which was investigated by Winstein and Adams (2), and Hafez, Halsey, and Wallis (3). One group of workers (2) studied the rate of formation of *i*-cholesterol from cholesteryl *p*-toluenesulfonate in glacial acetic acid containing various amounts of a base ion, while the other investigators (3) obtained the rates for various cholesteryl esters in a mixture of acetone, water, and potassium acetate. It was found that the rate of formation was first-order with respect to steroid ester over a wide range of temperatures and conditions. The formation of 3,5-cyclosterols, therefore, proceeds by a unimolecular ionic mechanism. Winstein (2) has shown in addition that the 5–6 ethylenic bond exerts a strong driving force on the formation of a carbonium ion. He therefore proposed the hybrid ion (I) as the intermediate in the rate determining step.



I

The acid rearrangement of 3,5-cyclosterols is also believed to be of the unimolecular type and to involve the same intermediate ion (I) (1, 2, 4–6); but so far, there is no direct evidence for this contention.

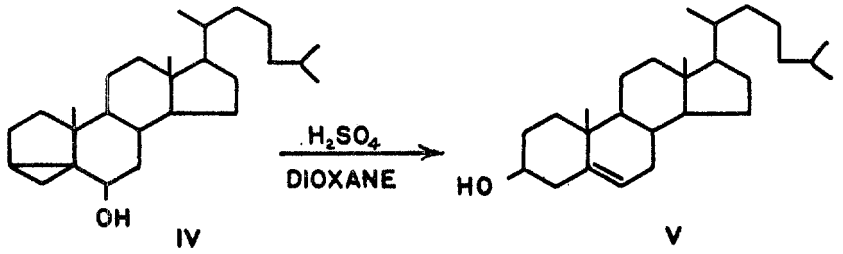
In this paper we wish to report on the kinetics of the acid rearrangement of 3,5-cyclocholestan-6β-ol (IV) to Δ^5-cholesten-3β-ol (V). A 3,5-cyclosteroid of the type II is known to rearrange quantitatively to III, where A^- can be Cl^-, Br^-, I^-, or AcO^- (1, 5, 7).



II III

The solvent most commonly used in these rearrangements is glacial acetic acid. When trace quantities of concentrated sulfuric acid are used, the rearranged product is the 3β-acetate, the acetate ion being furnished by the solvent.

Preliminary studies showed that, when the acid rearrangement is carried out in an inert solvent, such as dioxane, with various amounts of sulfuric acid, the free 3β-hydroxy compound is obtained directly. It was also found that the reaction goes to completion and is quantitative. This reaction, therefore, should give



IV V

a clear picture of the kinetics of the acid rearrangement *per se* since both the starting material (IV) and the rearranged product (V) have the same composition; no acid is consumed, no substitution occurs, and no by-products are formed.

TABLE I

FIRST ORDER RATE CONSTANTS FOR THE REARRANGEMENT OF 3,5-CYCLOCHOLESTAN-6β-OL IN SULFURIC ACID-DIOXANE MIXTUEES

CURVE IN FIGURE 1	TEMP., °C.	ACID CONC. c_A (moles × l^{-1})	RATE CONSTANT k' (sec^{-1})
○	30	2.45×10^{-3}	$0.98 \pm 0.01 \times 10^{-5}$
◔	30	2.79×10^{-2}	$1.07 \pm 0.03 \times 10^{-4}$
◒	30	5.57×10^{-2}	$1.82 \pm 0.02 \times 10^{-4}$
◉	30	11.14×10^{-2}	$5.95 \pm 0.13 \times 10^{-4}$
●	45	5.57×10^{-2}	$1.26 \pm 0.02 \times 10^{-3}$

If one follows the reaction by observing the change of optical rotation with time, a clean first-order reaction rate is obtained in every case. The difference in specific rotation is 119.8°, a value sufficiently large to produce accurate results. Substituting rotations for steroid concentrations, the rate equation takes the form

$$k't = \ln \frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty} - \text{const.}$$

In Figure 1 the values of $\ln \frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty}$ are plotted against time. The slope in each case is equal to the rate constant (Table I).

Since a temperature increase of only 15° causes an almost seven-fold increase of the rate under otherwise identical conditions, we were able to calculate the heat of activation $\Delta H^\ddagger$ for the acid rearrangement from the absolute rate equation (8):

$$k' = \frac{kT}{h} e^{-\Delta H^\ddagger/RT} e^{\Delta S^\ddagger/R}.$$

The heat of activation was found to be 24.0 ± 0.5 kcal with a $\Delta S^{\ddagger}_{30}{}^{\circ}$ of +3.5 ± 2 e.u. A comparison with Winstein's (2) $\Delta H^{\ddagger}$ of 24.4 ± 0.5 kcal and a $\Delta S^{\ddagger}_{35}{}^{\circ}$ of +0.5 ± 2 e.u. for the hydrolysis of cholesteryl *p*-toluenesulfonate supports

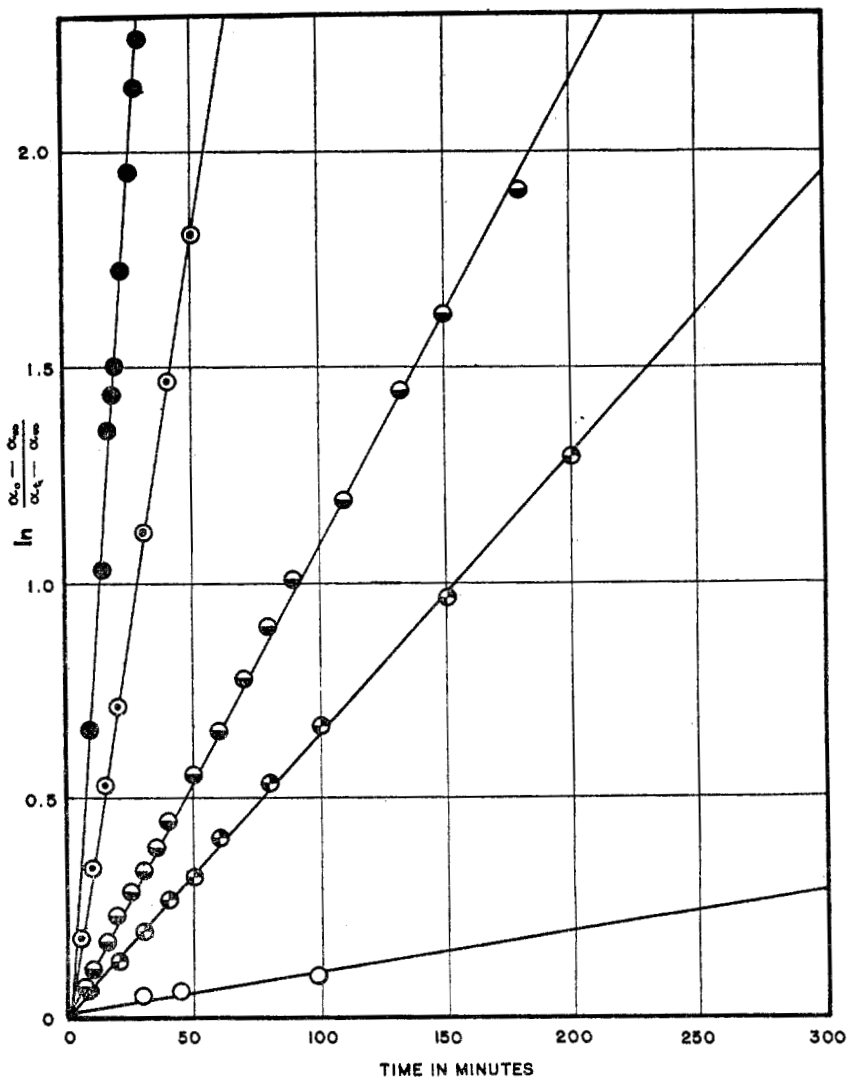


FIG. 1. FIRST-ORDER RATES OF 3,5-CYCLOCHOLESTAN-6β-OL AT VARIOUS SULFURIC ACID CONCENTRATIONS IN DIOXANE.

the concept of the same intermediate (I) in the rate determining step of either reaction.

Our investigation was next turned to the effect of acid concentration on the rate of rearrangement. The over-all rate can be expressed as

$$-\frac{d[\mathrm{Si}]}{dt} = K[\mathrm{Si}]^m[\mathrm{H}^+]^n \qquad \text{(i)}$$

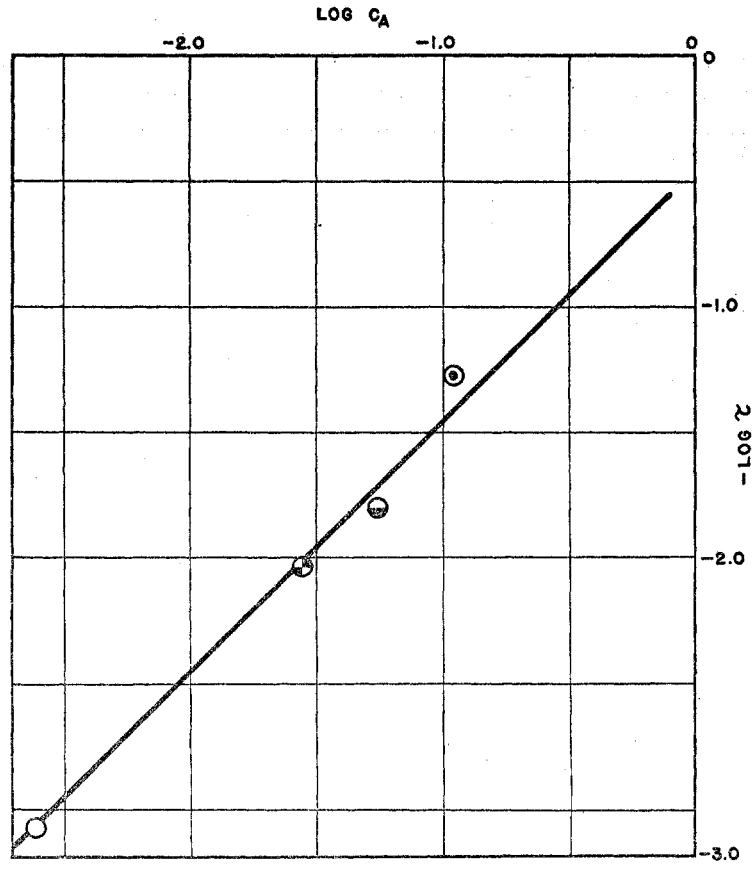


FIG. 2. FIRST-ORDER DEPENDENCE OF ACID CONCENTRATION ON THE REARRANGEMENT OF 3,5-CYCLOCHOLESTAN-6β-OL.

TABLE II

HALFTIMES τ FOR THE ACID REARRANGEMENT OF 3,5-CYCLOCHOLESTAN-6β-OL AT VARIOUS SULFURIC ACID CONCENTRATIONS c_A (Temp. 30°)

SYMBOL	τ (min.)	c_A (moles $\times$ l^{-1})	LOG τ	LOG c_A
○	1180	2.45×10^{-3}	3.072	−2.611
◔	106	2.79×10^{-2}	2.025	−1.555
◒	63.5	5.57×10^{-2}	1.803	−1.254
◉	18.9	11.14×10^{-2}	1.276	−0.953

where [Si] is the *i*-steroid concentration and $m = 1$, since the rate is first order with respect to steroid. Assuming that the acid concentration c_A is proportional to the hydrogen ion concentration $[H^+]$ over the range of concentrations studied

$$c_A = a[H^+] \qquad \text{(ii)}$$

TABLE III

ACIDITY FUNCTIONS OF SULFURIC ACID IN DIOXANE DETERMINED WITH *p*-NITROANILINE AS INDICATOR AT 353 mμ

c_A (moles $\times$ l^{-1})	LOG c_A	*H*
0.464	−0.33	−0.07
.279	−0.55	−0.40
.140	−0.86	−0.97
.070	−1.16	−1.52
.035	−1.46	−1.98
.017	−1.76	−2.44

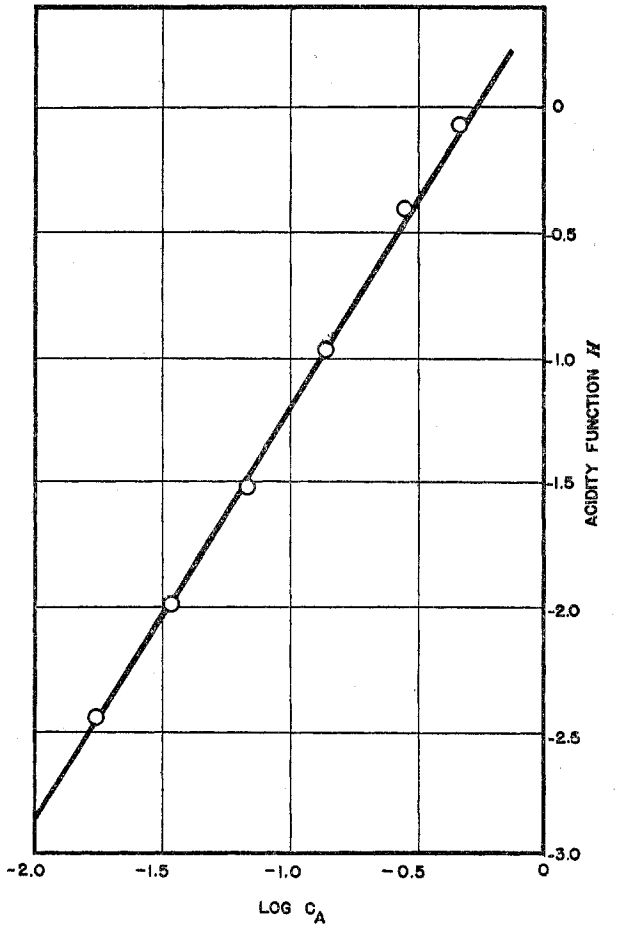


FIG. 3. CHANGE OF ACIDITY FUNCTION WITH ACID CONCENTRATION (Sulfuric Acid in Dioxane).

equation (i) on substitution and integration becomes

$$\ln \frac{[Si_0]}{[Si]} = K \left[\frac{c_A}{a}\right]^n t.$$

At half-time τ

$$\frac{[Si_0]}{[Si]} = 2$$

or

$$\tau = \left[\frac{\ln 2}{K} a^n\right] c_A^{-n} \qquad \text{(iii)}.$$

Writing equation (iii) in its logarithmic form, expression (iv) is obtained

$$-\log \tau = n \log c_A + A \qquad \text{(iv)}$$

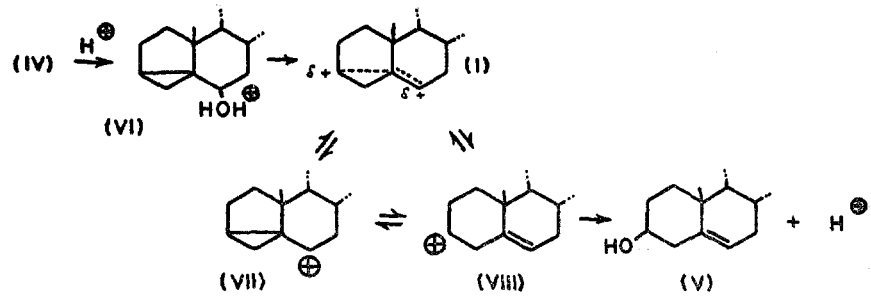
where all constants are contained in A. Plotting $-\log \tau$ *vs.* $\log c_A$, a straight line is obtained whose slope n is equal to unity (Figure 2). The values for τ, c_A, and their log-values are listed in Table II.

On the basis of the above results it can be concluded that the kinetics of the acid rearrangement of 3,5-cyclosteroids is a first-order reaction with respect to steroid and also a first-order reaction with respect to acid concentration; hence the over-all second-order rate equation (i) takes the form:

$$-\frac{d[Si]}{dt} = K[Si][H^+].$$

The assumption that the acid concentration is directly proportional to the hydrogen ion concentration (or the acidity function), was shown to be correct in a subsequent experiment. The acidity function H of sulfuric acid in dioxane was determined spectrophotometrically according to a method employed by Braude (9) for hydrochloric acid in dioxane. The results are listed in Table III and a plot in Figure 3 clearly shows that the acid concentration is directly proportional to the acidity function and hence to the hydrogen ion concentration (from 0.02 to 0.5 M in H_2SO_4).

Following directly from the kinetic data we wish to propose a mechanism which accounts well for the experimental facts. As in the course of ordinary carbonium ion formation, the hydroxyl group of the 3,5-cyclosterol (IV) is



protonated (VI) and removed. The limiting structure (VIII) of the intermediate carbonium ion (I) being favored in acidic medium, reacts with water to form the 3β-Δ⁵-steroid (V). Regeneration of the proton completes the reaction.

EXPERIMENTAL

Rate studies of the acid rearrangement in dioxane. Pure 3,5-cyclocholestan-6β-ol, m.p. 80.5–81.5°, $[\alpha]_D^{25}$ +80.9°, was prepared according to Wagner, *et al.* (1). The rotations were determined in a 2-dm. tube with a thermostated water-jacket; the steroid concentration was either *c*, 1.0 or 2.0. A stock solution of concentrated sulfuric acid in anhydrous dioxane was made up and standardized against 0.1 *N* sodium hydroxide. Aliquot portions of the acid

TABLE IV

EXPERIMENTAL DETAIL FOR THE ACID REARRANGEMENT OF 3,5-CYCLOCHOLESTAN-6β-OL. (c_A = 2.79 × 10^{-2} molar in H_2SO_4; Temp. 30°)

TIME, (min.)	α_t, (°)	$\frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty}$	10^4 k', (sec^{-1})
0	+3.20	1.00	—
5	+3.00	1.04	1.31*
10	+2.91	1.06	0.97*
20	+2.60	1.14	1.09
30	+2.34	1.22	1.11
40	+2.10	1.31	1.13
50	+1.93	1.38	1.07
60	+1.62	1.51	1.15*
80	+1.20	1.71	1.12
100	+0.95	1.94	1.11
150	+0.34	2.61	1.07
200	−0.15	3.60	1.07
320	−0.78	7.04	1.02
350	−0.90	8.60	1.03
390	−1.01	10.80	1.02
430	−1.09	13.25	1.09
490	−1.19	18.90	0.99*
1190	−1.44	—	—

$k' = 1.07 \pm 0.03 \times 10^{-4}$

were added to the steroid solutions in each run. The results are summarized in Table I (Figure 1). The rotational data for a typical run are listed in Table IV with the corresponding rate constants calculated for each point. Values with an asterisk are outside the mean deviation and are not included in the final value for the rate constant.

Spectrophotometric determination of the acidity function of sulfuric acid in dioxane. The extinction of various sulfuric acid mixtures in anhydrous dioxane, containing *p*-nitroaniline as indicator, was determined in a Beckman Spectrophotometer Model DU. For a detailed description of the method see Braude (9). The values for the acidity function *H* are listed in Table III (Figure 3).

SUMMARY

The rate of rearrangement of 3,5-cyclocholestan-6β-ol in various sulfuric acid — dioxane mixtures has been studied. The reaction was found to be first-order

with respect to both steroid and hydrogen ion concentration. The heat of activation for this rearrangement was found to be the same as that for the hydrolysis of cholesteryl *p*-toluenesulfonate, a fact which strongly supports the concept of the same intermediate for the two reactions. A mechanism for the over-all second-order reaction is proposed.

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