from ethylene glycol are more stable and are hydrolyzed less readily than those derived from 1,3-propanediol; and (c) the introduction of 2,2-dialkyl substituents into 1,3-propanediol increases the stability of, and decreases the hydrolysis rates of, the corresponding ketals. The latter effect is such that the ketals derived from 2,2-dimethyl- and 2,2-diethyl-1,3-propanediol are almost as stable as those derived from ethylene glycol and exhibit hydrolysis rates comparable to those of the corresponding ethylene ketals.

In the accompanying paper,[31] the above data will be used to evaluate the kinetic and equilibrium approaches to the selective ketalization of 5α-androstane-3,17-dione with the diols studied.

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(31) S. W. Smith and M. S. Newman, *J. Amer. Chem. Soc.*, **90**, 1253 (1968).

The *gem*-Dialkyl Effect. III. Kinetic and Equilibrium Studies of Steroid Cyclic Ketal Formation and Hydrolysis[1,2]

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Abstract: Kinetic and equilibrium data on steroid cyclic ketal formation and hydrolysis, reported in the accompanying paper,[4] are used as the basis of calculations which compare the kinetic (acid hydrolysis of bisketal) and equilibrium (equilibration of dione and glycol) approaches to the selective ketalization of glycols. The kinetic and equilibrium data indicate that (1) the 17-cyclic ketals are formed less readily and are hydrolyzed at a faster rate than the corresponding 3-ketals; (2) the ketals derived from ethylene glycol are formed more readily and are hydrolyzed more slowly than those derived from 1,3-propanediol; and (3) *gem*-dialkyl substitution in 1,3-propanediol promotes cyclic ketal formation and decreases the rates of hydrolysis of the corresponding ketals.

A study[5] of the formation and hydrolysis of the ketals of cyclopentanone, 2-methylcyclopentanone, and cyclohexanone derived from ethylene glycol, 1,3-propanediol, and several 2,2-dialkyl-1,3-propanediols indicated that the latter might serve as effective ketalizing agents in the steroid field. The somewhat limited equilibrium data obtained[5] indicated that equilibration of the ketone and ketalizing agent merited consideration as an approach to the selective ketalization of polyketonic steroids. A lack of sufficient kinetic and thermodynamic data on steroid ketal formation and hydrolysis has prevented a comparison of the kinetic and equilibrium approaches to the selective ketalization of such steroids. The objectives of the present investigation were (a) to determine whether a typical steroid dione, such as 5α-androstane-3,17-dione (I), could be selectively ketalized in higher yields by equilibration of I with the ketalizing agent (equilibrium approach), or by the acid hydrolysis of the corresponding 3,17-bisketal (kinetic approach); and (b) to determine the effect of *gem*-dialkyl substitution in the ketalizing agent on the selectivity of each of these approaches. To these ends, equilibrium data obtained[4] were used to compute product distributions as a function of the ratio of initial glycol to dione concentrations for equilibria involving I and ethylene glycol, 2,2-dimethyl-1,3-propanediol, and 2,2-diethyl-1,3-propanediol[6] and the kinetic data obtained[4] were used to compute product distributions as a function of time for the acid hydrolysis of the corresponding 3,17-bisketals of I.

Mathematical Evaluation of the Equilibrium Approach

The equilibria involved are shown below (R varies as the structure of the glycol used).

$$\text{dione} + \text{glycol} \overset{K_A}{\rightleftarrows} \text{3-ketal 17-one} + H_2O \qquad (1)$$

$$\text{dione} + \text{glycol} \overset{K_B}{\rightleftarrows} \text{17-ketal 3-one} + H_2O \qquad (2)$$

$$\text{3-ketal 17-one} + \text{glycol} \overset{K_{CA}}{\rightleftarrows} \text{3,17-bisketal} + H_2O \qquad (3)$$

$$\text{17-ketal 3-one} + \text{glycol} \overset{K_{CB}}{\rightleftarrows} \text{3,17-bisketal} + H_2O \qquad (4)$$

A mathematical evaluation of the equilibrium approach to the selective ketalization of the dione I should enable one to determine which glycol and what initial glycol to dione ratio would give optimum yields or ratios of 3-ketal 17-one, which is considered to be the desired product. These objectives were met by use of experimental equilibrium constants[4] and the computer facilities of The Ohio State University Numerical Computations Laboratory.[7]

The computer input consisted of the equilibrium concentrations of dione (D), 3-ketal 17-one (A), 17-ketal 3-one (B), and 3,17-bisketal (C) and the initial water

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(1) This investigation was supported in part by a grant from the Holland-Rantos Co., New York, N. Y., and by Grant GP6224 of the National Science Foundation, which are gratefully acknowledged.

(2) This work was taken from the Ph.D. dissertation of S. W. S., submitted to the Chemistry Department, 1967.

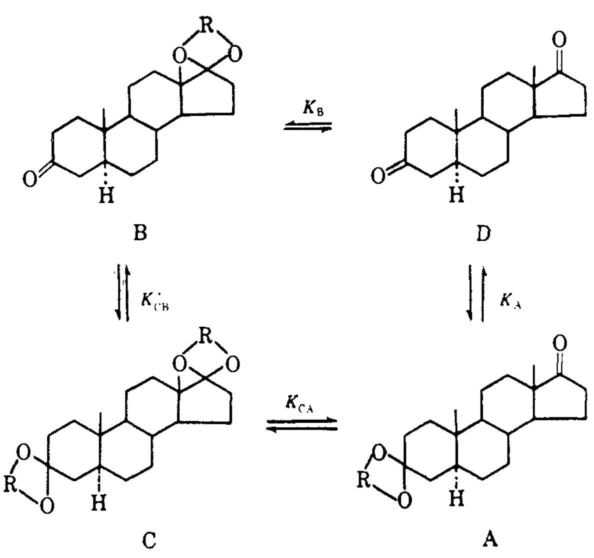
(3) To whom all correspondence should be addressed.

(4) S. W. Smith and M. S. Newman, *J. Amer. Chem. Soc.*, **90**, 1249 (1968).

(5) M. S. Newman and R. J. Harper, Jr., *ibid.*, **80**, 6350 (1958): paper I of this series.

(6) Data on the formation and hydrolysis of ketals of I derived from 1,3-propanediol indicate that the use of this diol offers no advantages in the selective ketalization of I, and calculations involving this diol are therefore omitted.

(7) The use of these computer facilities is gratefully acknowledged. Thanks are also due Dr. G. Dyer for helpful suggestions concerning the computer programming involved. Copies of the computer programs are available upon request from S. W. S.



$(W_0)^8$ and glycol (G_0) concentrations from three or four equilibrium runs involving dimethoxyethane.[4] All concentrations were expressed as molar per cent. From these data, the equilibrium water (W) and glycol (G) concentrations and the equilibrium constants K_A, K_B, K_{CA}, and K_{CB} were computed by use of the relationships given in eq 5–10

$$W = W_0 + A + B + 2C \tag{5}$$

$$G = G_0 - A - B - 2C \tag{6}$$

$$K_A = \frac{(\text{3-ketal 17-one})(H_2O)}{(\text{3,17-dione})(\text{glycol})} = \frac{A(W_0 + A + B + 2C)}{D(G_0 - A - B - 2C)} \tag{7}$$

$$K_B = \frac{(\text{17-ketal 3-one})(H_2O)}{(\text{3,17-dione})(\text{glycol})} = \frac{B(W_0 + A + B + 2C)}{D(G_0 - A - B - 2C)} \tag{8}$$

$$K_{CA} = \frac{(\text{3,17-bisketal})(H_2O)}{(\text{3-ketal 17-one})(\text{glycol})} = \frac{C(W_0 + A + B + 2C)}{A(G_0 - A - B - 2C)} \tag{9}$$

$$K_{CB} = \frac{(\text{3,17-bisketal})(H_2O)}{(\text{17-ketal 3-one})(\text{glycol})} = \frac{C(W_0 + A + B + 2C)}{B(G_0 - A - B - 2C)} \tag{10}$$

where K_A = equilibrium constant for formation of the 3-ketal 17-one from the 3,17-dione; K_B = equilibrium constant for formation of the 17-ketal 3-one from the 3,17-dione; K_{CA} = equilibrium constant for formation of the 3,17-bisketal from the 3-ketal 17-one; K_{CB} = equilibrium constant for formation of the 3,17-bisketal from the 17-ketal 3-one.

The equilibrium constants from the individual runs were averaged and these average values were used to compute equilibrium concentrations of A, B, C, and D in runs involving various ratios of initial glycol to dione concentrations. Although constants for the various equilibrium runs with the dione and a given glycol varied as much as 10–15% with changing initial glycol concentrations, the use of average values in these computations appears justified by the close agreement between computations based on average and individual equilibrium constants.

Calculation Methods. Division of eq 7 by eq 8 gives the relationship in eq 11 or 12 between the equilibrium

$$A/B = K_A/K_B \tag{11}$$

$$B = (K_B/K_A)A \tag{12}$$

concentrations of A and B. Substitution of this value of B into eq 9 and solving for C yields the quadratic eq 13. The desired root was found to be of the

$$2C^2 + [A(1 + K_B/KA) + W_0 + 2A(K_{CA})]C + K_{CA}[A^2(1 + K_B/KA) - AG_0] = 0 \tag{13}$$

form given in eq 14

$$C = \frac{-Y + \sqrt{Y^2 - 4XZ}}{2X} \tag{14}$$

where $X = 2$, $Y = A(1 + K_B/KA) + W_0 + 2A(K_{CA})$, and $Z = K_{CA}[A^2(1 + K_B/KA) - AG_0]$. The equilibrium concentration of D may be represented by eq 15. The

$$D = D_0 - A - B - C = 100 - A - B - C \tag{15}$$

equilibrium concentrations of B, C, and D may therefore be related to that of A and the initial water and glycol concentrations. The values of A, B, C, and D corresponding to various initial glycol to dione ratios were obtained by determining that value of A which when substituted into eq 7 would, along with the corresponding values of B, C, and D calculated by means of eq 12, 14, and 15, respectively, give a value of K_A very close to the experimental value. The computer program was designed so that for each glycol to dione ratio, trial values of A were selected and used to compute corresponding trial values of B, C, and D. Each set of trial values was substituted into eq 7, to give a trial value of K_A, which was compared with the experimental value. If this value was within 95–105% of the experimental value, the corresponding values of A, B, C, and D were printed out as the equilibrium product distribution for that particular glycol to dione ratio. If the trial value of K_A was not within these limits, the next higher trial value of A was tested as above until an acceptable value was found. In this manner, product distributions were computed as a function of initial glycol to dione ratios for equilibria involving I and ethylene glycol, 2,2-dimethyl-1,3-propanediol, and 2,2-diethyl-1,3-propanediol. The computations were for equilibria conducted in 1,2-dimethoxyethane at 50° and catalyzed by *p*-toluenesulfonic acid monohydrate. The results of these computations are shown in Figures 1–3 and summarized in part in Table I.

Discussion

In the selective ketalization of I with the glycols studied, the 3-ketal 17-one is considered to be the desired monoketal. Attempts to separate mixtures of the dione, 3-ketal 17-one, 17-ketal 3-one, and 3,17-bisketal by paper, thin layer, and gas–liquid partition chromatography indicated separation of the isomeric monoketals to be the most difficult. A favorable product distribution is therefore one in which optimal yields

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[8] The initial water concentration arises as a result of the use of *p*-toluenesulfonic acid monohydrate as catalyst in these equilibria.

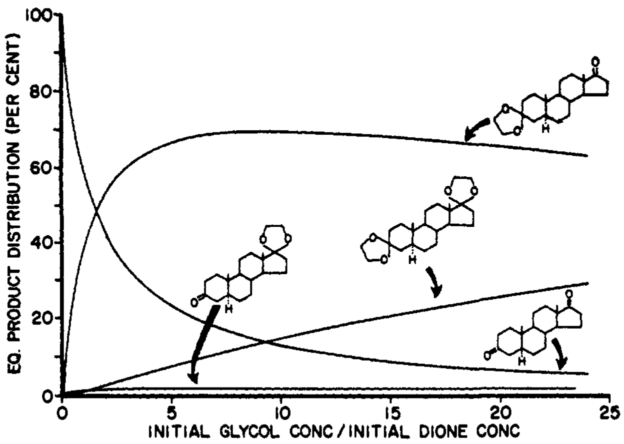


Figure 1. Equilibria in the system 5α-androstane-3,17-dione and 1,2-ethanediol: temperature = 50°; solvent = glyme.

of the 3-ketal 17-one are obtained along with minimal amounts of the isomeric 17-ketal 3-one.

The data in Figures 1–3 illustrate the following points of interest regarding equilibria between the dione and the glycols studied.

Table I. Summary of Calculated Product Distributions for Equilibria Involving 5α-Androstane-3,17-dione and Various Glycols

Glycol	G_0/D_0[a]	A[b]	B[b]	C[b]	D[b]
Ethylene	6	67.5	2.2	9.5	20.8
	9	69.1	2.2	13.9	14.8
	12	68.6	2.2	17.8	11.4
	15	67.4	2.2	21.8	9.2
	18	65.9	2.1	24.3	7.7
2,2-Dimethyl-1,3-propylene	6	69.1	...	2.6	28.3
	9	74.6	...	4.0	21.4
	12	77.5	...	5.3	17.2
	15	79.0	...	6.6	14.4
	18	79.7	...	7.9	12.4
2,2-Diethyl-1,3-propylene	6	73.9	...	1.1	25.0
	9	79.6	...	1.8	18.6
	12	82.8	...	2.5	14.7
	15	84.6	...	3.2	12.2
	18	85.8	...	3.8	10.4

[a] G_0/D_0 = ratio of initial glycol to dione concentrations. [b] A, B, C, D = calculated equilibrium concentrations of 3-ketal 17-one, 17-ketal 3-one, 3,17-bisketal, and 3,17-dione, respectively, in molar per cent.

1. Higher yields of the 3-ketal 17-one may be obtained by use of the 2,2-dialkyl-1,3-propanediols than by the use of ethylene glycol.
2. The use of the 2,2-dialkyl-1,3-propanediols yields very little, if any, of the isomeric 17-ketal 3-one.
3. In all cases, the concentration of the 3-ketal 17-one becomes relatively insensitive to increases in the glycol to dione ratio at ratios of 10 and higher.
4. Increasing this ratio beyond 10 does lead to more 3,17-bisketal and less 3,17-dione, and one may select a ratio most favorable for isolation and purification of the desired monoketal.
5. Of the glycols studied, 2,2-diethyl-1,3-propanediol gives the highest yields of 3-ketal 17-one and the lowest amounts of contaminating side products.

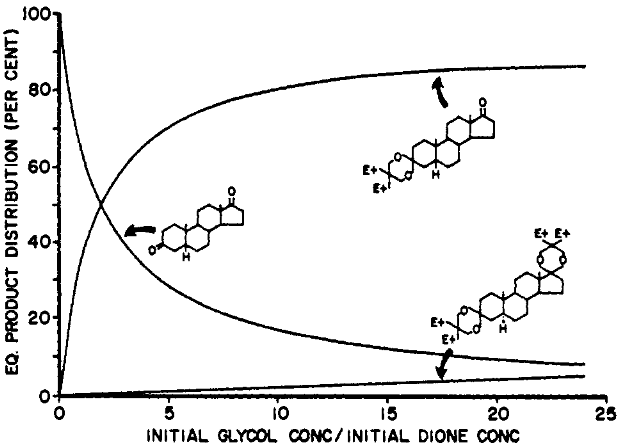


Figure 2. Equilibria in the system 5α-androstane-3,17-dione and 2,2-diethyl-1,3-propanediol: temperature = 50°; solvent = glyme.

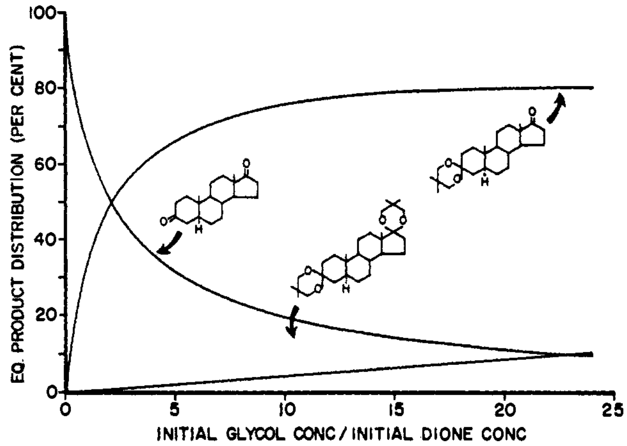


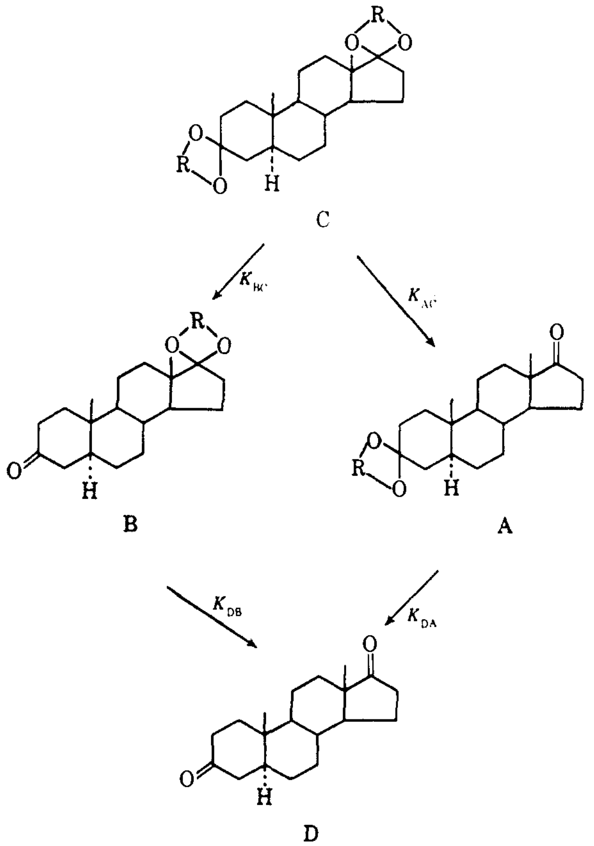
Figure 3. Equilibria in the system 5α-androstane-3,17-dione and 2,2-dimethyl-1,3-propanediol: temperature = 50°; solvent = glyme.

It may be concluded from the above that the use of 2,2-dimethyl- or 2,2-diethyl-1,3-propanediol in these equilibria results in a product distribution which is more favorable for the formation and isolation of the 3-ketal 17-one than the use of ethylene glycol.

In order to test the computed product distributions and the equilibrium constants upon which they are based, equilibria between the test dione and the two 2,2-dialkyl-1,3-propanediols were conducted using glycol to dione ratios of 14. The observed (glpc) product distributions showed excellent agreement with the computed values. The observed product distribution in the case of 2,2-dimethyl-1,3-propanediol was A = 77.2% (calcd 78.6), C = 6.2% (calcd 6.2), and D = 16.6% (calcd 15.2), while that in the case of 2,2-diethyl-1,3-propanediol was A = 83.2% (calcd 84.1), C = 6.1% (calcd 2.9), and D = 10.7% (calcd 13.0).

An isolation experiment was conducted in order to evaluate the utility of the equilibrium approach in converting the dione into the 3-ketal 17-one. A mixture of 5 g (0.017 mol) of 5α-androstane-3,17-dione, 45.8 g (0.34 mol) of 2,2-diethyl-1,3-propanediol, and 0.8 g of *p*-toluenesulfonic acid monohydrate in 1 l. of 1,2-dimethoxyethane was equilibrated at 50° in a sealed flask for 3 days. The reaction was quenched by the addition of 2 ml of triethylamine and the solvent was removed under reduced pressure at 30°. The resulting dark yellow oil was taken up in 100 ml of ether–benzene (1:1) and this solution was washed with three 25-ml aliquots of water. The combined washings were extracted with two 15-ml portions of ether–benzene (1:1) and the combined organic phases were dried by filtration through $MgSO_4$. The filtrate was evaporated under reduced pressure and the resulting pale yellow oil was taken up in 50 ml of acetone. After standing overnight at room temperature, the solution had deposited a small amount (0.35 g) of a white material which was collected by filtration and was found to be the 3,17-bisketal by glpc analysis. The filtrate was seeded with authentic 3,3-(2,2-diethyltrimethylenedioxy)-5α-androstan-17-one[4] and stored in the cold. After 24 hr, the resulting precipitate was collected and air dried to give 4.7 g of white material, mp 165–170°. Gas chromatographic analysis of the material indicated it to consist of about 94% 3-ketal 17-one, 5% 3,17-dione, and 1% 3,17-bisketal. An additional crystallization of 4.5 g of this material from acetone (50 ml) in the cold gave 3.6 g (62% of theoretical based on computed product distributions) of the 3-ketal 17-one (mp 174–177°, carbonyl absorption at 1743 cm^{-1})[9] which was found to be contaminated with about 1% of the dione by chromatographic analysis.

Mathematical Evaluation of the Kinetic Approach. The set of reactions under consideration may be represented as (R varies as the structure of the glycol used)



where k_{AC} is the pseudo-first-order rate constant for formation of the 3-ketal 17-one (A) from the 3,17-bisketal (C), k_{BC} is the corresponding constant for formation of the 17-ketal 3-one (B) from the bisketal, and k_{DA} and k_{DB} are the corresponding rate constants for formation of the 3,17-dione (D) from monoketals A and B, respectively.

A mathematical evaluation of the kinetic approach to the selective ketalization of 5α-androstane-3,17-dione should provide answers to the following questions. During the acid hydrolysis of a 3,17-bisketal derived from the dione and a given glycol, how does the product distribution vary with time? Is there a time at which the reaction may be quenched and worked up to give a selectively ketalized product in high yield? Moreover, would the use of a bisketal derived from a particular glycol be more advantageous than the use of a bisketal derived from one of several other available glycols?

Answers to the above questions were obtained by use of the experimental values[4] of k_{AC}, k_{BC}, k_{DA}, and k_{DB}[10] and eq 16–19.

$$C_t = (100)e^{-(k_{AC} + k_{BC})t} \tag{16}$$

$$A_t = \frac{(100)k_{AC}}{k_{DA} - k_{AC} - k_{BC}} e^{-(k_{AC} + k_{BC})t} - e^{-k_{DA}t} \tag{17}$$

$$B_t = \frac{(100)k_{BC}}{k_{DB} - k_{AC} - k_{BC}} e^{-(k_{AC} + k_{BC})t} - e^{-k_{DB}t} \tag{18}$$

$$D_t = 100 - A_t - B_t - C_t \tag{19}$$

The expressions for A_t, B_t, and C_t were obtained by integration of the rate expressions (eq 20–22) by the integration factor method,[11] after defining $C_0 = 100$ and $A_0 = B_0 = D_0 = 0$.

$$\frac{dC}{dt} = -(k_{AC} + k_{BC})C \tag{20}$$

$$\frac{dA}{dt} = k_{AC}C - k_{DA}A \tag{21}$$

$$\frac{dB}{dt} = k_{BC}C - k_{DB}B \tag{22}$$

Product distributions were computed[7] as a function of time for the acid hydrolysis of the 3,17-bisketals of I derived from ethylene glycol, 2,2-dimethyl-1,3-propanediol, and 2,2-diethyl-1,3-propanediol. The computations are for reactions conducted at 37° in 4:1 (v/v) dioxane–water, 0.02 *N* in HCl. The results of these computations are given in Figures 4–6 and summarized in part in Table II.

Table II. Computed Product Distributions for the Acid Hydrolysis of the Bisketals Derived from 5α-Androstane-3,17-dione and Various Glycols

Glycol	T_{max}[a]	A[b]	B[b]	C[b]	D[b]
Ethylene	60	33.0	18.6	19.6	28.8
2,2-Dimethyl-1,3-propylene	26	58.5	6.9	11.2	23.4
2,2-Diethyl-1,3-propylene	68	56.7	8.1	10.1	25.1

[a] The time (minutes) at which the hydrolysis reaction should be quenched and worked up in order to obtain a maximal yield of the desired 3-ketal 17-one. [b] *A*, *B*, *C*, *D* = concentrations in molar per cent of the 3-ketal 17-one, 17-ketal 3-one, 3,17-bisketal, and 3,17-dione, respectively.

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[9] An analytical sample of the authentic 3-ketal 17-one had mp 177.0–177.7°.

[10] k_{AC} and k_{BC} were assumed to be approximately equal to the rate constants for hydrolysis of the corresponding ketals of 5α-androstan-17-one and 5α-androstan-3-one, respectively.

[11] L. R. Ford, "Differential Equations," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1955, Chapter 2.

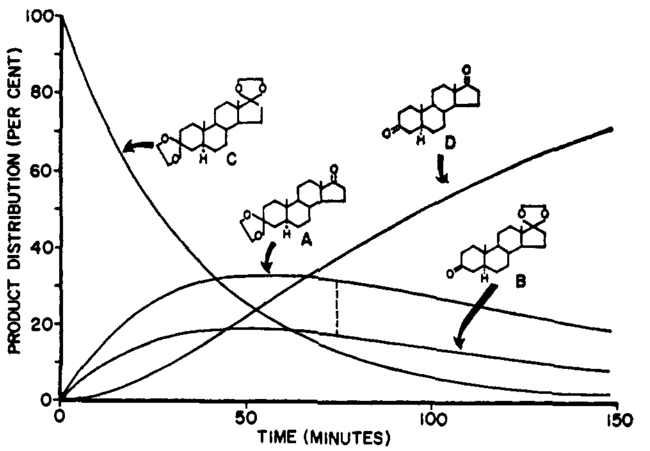

Figure 4. Acid hydrolysis of the bisketal derived from 5α-androstane-3,17-dione and 1,2-ethanediol: temperature = 37°; solvent = 80:20 dioxane-water; (HCl) = 0.02 *N*.

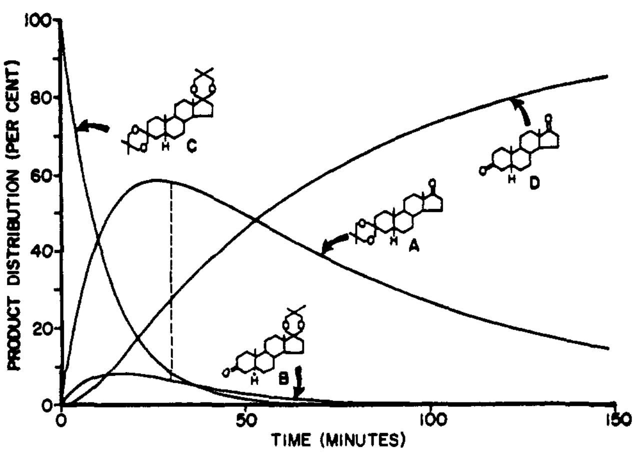

Figure 5. Acid hydrolysis of the bisketal derived from 5α-androstane-3,17-dione and 2,2-dimethyl-1,3-propanediol: temperature = 37°; solvent = 80:20 dioxane-water; (HCl) = 0.02 *N*.

Discussion

As was pointed out earlier, a favorable product distribution in the selective ketalization of the dione is one in which a high yield of the 3-ketal 17-one is obtained, along with minimal amounts of 17-ketal 3-one, 3,17-bisketal, and 3,17-dione.

The computed product distributions in the case of the kinetic approach indicate the following.

(1) Higher yields of the desired monoketal may be obtained by partial hydrolysis of the 2,2-dialkyl-1,3-propylene ketals than by partial hydrolysis of the ethylene ketals.

(2) In all cases, the 3-ketal 17-one is contaminated with significant amounts of the 17-ketal 3-one, but this contamination is less in the case of the 2,2-dialkyl-1,3-propylene ketals.

(3) In order to obtain a product distribution favorable for the formation and isolation of the desired monoketal, the hydrolysis reaction must be quenched at the proper time or the distribution may become less favorable by continued reaction. The vertical lines in Figures 4, 5, and 6 indicate the recommended times to stop hydrolysis if maximum ease of isolation of desired monoketal is the goal.

In conclusion, if it is assumed that the 3-ketal 17-one is the desired monoketal, the above calculations indicate the following.

(1) The use of 2,2-dimethyl- or 2,2-diethyl-1,3-propanediol or the corresponding 3,17-bisketals increases the selectivity of both the kinetic and equilibrium approaches to the selective ketalization of 5α-androstane-3,17-dione.

(2) The equilibrium approach is far superior to the kinetic approach from the standpoint of higher yields of the desired monoketal and less contamination with side products. In this respect, 2,2-diethyl-1,3-propanediol is superior to 2,2-dimethyl-1,3-propanediol, both of which are superior to ethylene glycol, which presently is the glycol of choice for ketalization.

In addition to giving a less favorable product distribution than the equilibrium approach, the kinetic approach involves the synthesis and isolation of an intermediate bisketal and the hydrolysis reaction must be followed closely and quenched at the proper time. The equilibrium approach, on the other hand, gives a better product distribution and involves no synthesis of intermediates, and the reaction may be worked up at leisure. Furthermore, in the latter approach the glycol to dione ratio may be varied so as to optimize conditions for isolation of the desired monoketal.

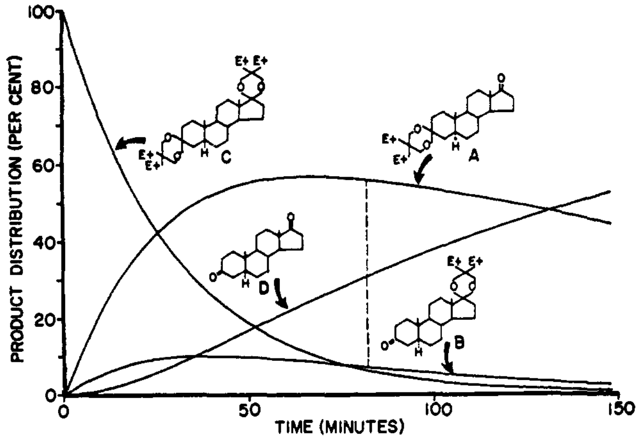

Figure 6. Acid hydrolysis of the bisketal derived from 5α-androstane-3,17-dione and 2,2-diethyl-1,3-propanediol: temperature = 37°; solvent = 80:20 dioxane-water (HCl) = 0.02 *N*.

One objection which might be raised concerning the latter approach is that, being an *equilibrium* process, long reaction times might be encountered. However, for practical purposes, equilibrium is attained in these reactions in 1-2 days or less under the reaction conditions employed.[4] The synthesis, isolation, and hydrolysis of a bisketal would take at least this long.

In conclusion it should be emphasized that although the results described above have been obtained for only one diketone, the principles involved should apply to any problem involving selective ketalization. In particular, the much more favorable proportion of desired monoketal obtainable by using the equilibrium approach should be emphasized since in all previous work the kinetic approach has been the method of choice. Furthermore, 2,2-dimethyl-1,3-propanediol and 2,2-diethyl-1,3-propanediol offer distinct advantage over the use of ethylene glycol, which to date has been the glycol of choice in ketalizations.[12]

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(12) We would like to thank Professor Jack Hine for his help in checking the kinetic and thermodynamic calculations involved in this and the accompanying paper.