The *gem*-Dialkyl Effect. II. A Comparison of the Kinetic and Equilibrium Approaches to the Selective Ketalization of 5α-Androstane-3,17-dione with Various Glycols[1,2]

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Abstract: Rate constants for the acid hydrolysis of cyclic ketals of 5α-androstane-3,17-dione, 5α-androstan-3-one, and 5α-androstan-17-one derived from ethylene glycol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, and 2,2-diethyl-1,3-propanediol are reported, as well as equilibrium constants for the acid-catalyzed reaction of 5α-androstane-3,17-dione (I) with ethylene glycol, 2,2-dimethyl-1,3-propanediol, and 2,2-diethyl-1,3-propanediol. The calculations indicate that the use of the 2,2-dialkyl-1,3-propanediols, or the bisketals derived therefrom, increases the selectivity of both the kinetic and equilibrium approaches. The calculations also illustrate the superiority of the equilibrium approach in the conversion of I to the 3-ketal 17-one.

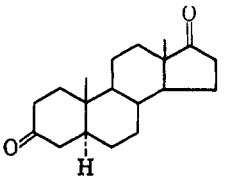
The reactivity of ketone functions under many of the reaction conditions employed in chemical transformations often necessitates their protection, commonly by ketal formation. The utility of this method lies in the stability of ketals under a wide variety of reaction conditions and the facile regeneration of the ketone function by mild acid hydrolysis.

The protection of ketone functions by ketal formation has been of particular importance in the transformation of steroids. Steroid ketals may be prepared by refluxing the ketone with excess mono- or dihydric alcohol and an acid catalyst in a solvent such as benzene, toluene, or xylene with distillative removal of the water formed (direct ketalization).[4] Alternatively, a mixture of the steroid ketone, acid catalyst, and the ethylene ketal of acetone or butanone may be distilled (exchange ketalization).[5] In addition to the ethylene ketals of acetone and butanone, those of mesityl oxide[6] and 2-dimethylamino-1,3-dioxolane[7] have been used for the transketalization of steroid ketones. Ethylene glycol is the only glycol to find widespread use as a ketalizing agent in the steroid field and the use of other glycols has not been fully explored.

The polyfunctional character of many steroids and the variety of reactions to which they are subjected often necessitate the selective ketalization of polyketonic steroids. The general approach to the selective ketalization of such steroids has been kinetic in nature. Both the direct and exchange methods of selective steroid ketal formation are based on reactivity differences between ketone functions in the polyketonic steroid. The selective acid hydrolysis of steroid polyketals, also widely used for selective steroid ketal formation, is based on the relative rates of hydrolysis of the ketals.[8] While these kinetic methods have been successfully employed for the selective ketalization of polyketonic steroids in which the ketone functions differ widely in their reactivity toward ketalization, the use of these methods for the ketalization of steroids in which the ketone functions are of similar reactivity has given mixtures of isomeric ketals from which it has often been difficult to isolate the desired ketal in good yield.[9-11]

One approach to the selective ketalization of polyketonic steroids which appears to have been neglected is an equilibrium approach in which the ketone is equilibrated with the ketalizing agent and an acid catalyst.

The paucity of data on the effect of the structure of the ketalizing agent on steroid cyclic ketal formation and hydrolysis prompted the present investigation. A study of the formation and hydrolysis of cyclic ketals of cyclohexanone, cyclopentanone, and 2-methylcyclopentanone[12] indicated that 2,2-dimethyl- and/or 2,2-diethyl-1,3-propanediol might serve as effective ketalizing agents in the steroid field. The objectives of the present investigation were (a) to determine whether a typical steroid dione, such as 5α-androstane-3,17-dione (I), can best be selectively ketalized by equilibration of the dione and the ketalizing agent (equilibrium approach), or by the acid hydrolysis of the corresponding bisketal (kinetic approach), and (b) to determine the effect of *gem*-dialkyl substitution in the ketalizing agent on the selectivity of either or both of these approaches. To



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

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Table I. Yields and Physical Properties of New Ketals of the 5α-Androstane Series

Ketal[a] function at 3-	17-	Yield, %	Mp,[b] °C	Specific rotation,[c] deg	Calcd, %[d] C	Calcd, %[d] H	Found, %[d] C	Found, %[d] H
P	P	71	187.0–187.8	−3.6	74.4	9.9	74.4	9.9
P	β-OH	88	156.0–156.9	+3.1	76.0	10.3	75.9	10.4
P	one	86	155.5–156.5	+73.7	76.1	9.8	75.9	9.9
β-OH	P	82	161.9–162.9	+1.1	76.0	10.3	75.8	10.5
one	P	85	149.5–150.6	+11.0	76.1	9.8	76.0	9.7
P	S	82	94.6–95.8	−31.3	79.6	10.8	79.3	10.7
S	P	79	98.0–99.2	−2.4	79.6	10.8	79.5	10.9
M_2P	M_2P	73	164.0–165.2	−25.8	75.6	10.5	75.7	10.6
M_2P	β-OH	74	208.0–209.1	−39.6	76.8	10.5	76.6	10.4
M_2P	one	75	211.9–213.0	+41.9	77.0	10.2	77.1	10.1
β-OH	M_2P	84	165.6–166.2	−31.3	76.8	10.5	76.7	10.4
one	M_2P	76	163.0–164.2	−15.4	77.0	10.2	77.2	10.1
M_2P	S	59	163.0–164.5	−5.3	80.1	11.1	79.8	11.1
S	M_2O	61	120.0–121.2	−8.5	80.1	11.1	80.0	11.2
E_2P	E_2P	72	109.0–110.3	−4.0	76.8	10.9	76.7	10.8
E_2P	β-OH	67	160.5–161.7	+4.4	77.3	10.9	77.2	10.7
E_2P	one	75	177.0–177.7	+62.5	77.7	10.4	77.5	10.4
β-OH	E_2P	83	150.5–151.2	−3.6	77.3	10.9	77.1	10.8
one	E_2P	50	138.3–139.6	+11.4	77.7	10.4	77.5	10.2
E_2P	S	66	121.0–122.0	−5.8	80.5	11.3	80.2	11.2
S	E_2P	84	129.5–130.8	+3.4	80.5	11.3	80.3	11.2

[a] P = 1,3-propylene ketal, M_2P = (2,2-dimethyl)-1,3-propylene ketal, E_2P = (2,2-diethyl)-1,3-propylene ketal, β-OH = β-hydroxyl group, S = saturated, and one = ketone group. [b] Melting points were taken with a Hershberg apparatus using Anschuetz short-stem thermometers: E. B. Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 312 (1936). [c] Specific rotations were measured at the D line of sodium as 5–10% solutions in chloroform at 25–27°. The instrument used was a Franz, Schmidt, and Haensch No. 7397 polarimeter and the cell length was 10 cm. [d] Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

this end, rate constants for the acid hydrolysis of, and equilibrium constants for the formation of, ketals of the 5α-androstane series derived from ethylene glycol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, and 2,2-diethyl-1,3-propanediol were determined.

Experimental Section

A. Synthesis of Steroid Cyclic Ketals. Ethylene glycol and 1,3-propanediol were purified by distillation, while 2,2-dimethyl-1,3-propanediol (mp 128.0–129.1°) and 2,2-diethyl-1,3-propanediol (mp 61.0–61.8°) were purified by recrystallization from benzene and petroleum ether (bp 65–70°), respectively. Benzene was purified as described.[13] The 5α-androstane-3,17-dione (mp 132.3–134.0°)[14] was used as received (G. D. Searle).

The cyclic ketals were prepared by the direct ketalization method,[4] in which a mixture of the ketone, glycol, and *p*-toluenesulfonic monohydrate in benzene was refluxed with a Dean–Stark phase-separating head and the water was removed as formed. The cooled reaction mixture was diluted with an equal volume of ether and this mixture was washed with 10% sodium carbonate solution and then with water until the washings were neutral to litmus. The washed organic layer was dried by filtration through anhydrous magnesium sulfate and evaporated to near dryness under reduced pressure. The resulting residue was purified by crystallization from an appropriate solvent. The monoketals of 5α-androstane-3,17-dione were prepared by ketalization of 5α-androstan-3-on-17β-ol and the corresponding 17-on-3β-ol, followed by chromic acid–pyridine oxidation to the corresponding ketal-one. The yields and physical properties of the new ketals are given in Table I.

5α-Androstan-3-one (mp 104.5–105.5°) was prepared in 91% yield as previously described.[15] In a completely analogous manner, 5α-androstan-17-one (mp 120.5–121.7°) and $[\alpha]^{25}D$ +93° (*c* 1, chloroform) was prepared from 5α-androstan-17β-ol-3-one in two steps in an over-all yield of 90%.

B. Hydrolysis of Steroid Cyclic Ketals. The acid hydrolysis of the cyclic ketals in 4:1 (v/v) *p*-dioxane–water at 37° was followed with a Beckman DU spectrophotometer equipped with thermospacers.

In each experiment, 1 ml of 0.1 *N* HCl and an aliquot of a stock solution of ketal in dioxane were diluted to 5 ml with dioxane at 37°.[16] A portion of this solution was transferred to a 1-cm quartz cell which was placed in the cell compartment of the spectrophotometer for the course of the reaction. Water was pumped through the jacketed cell compartment from a water bath maintained at 37 ± 0.05° and the cell temperature never differed from that of the water bath by more than 0.1°. After waiting a short time for thermal equilibrium to be attained in the cell compartment, the optical density of the reaction mixture at 280 mμ was measured against a blank of 4:1 (v/v) dioxane–water, 0.02 *N* in HCl, at convenient intervals until constant. The use of 4:1 dioxane–water as solvent was dictated by the solubility limits of the ketals and by the requirement of maintaining a high (*ca.* 1000) ratio of initial water to ketal concentrations. Under these reaction conditions, pseudo-first-order kinetics were observed.

The absorbance of standard solutions of 5α-androstane-3,17-dione was measured at 280 mμ in 4:1 (v/v) dioxane–water, 4:1 dioxane–water 0.012 *M* in 2,2-dimethyl-1,3-propanediol, and 4:1 dioxane–water 0.012 *M* in the above diol and 0.02 *N* in HCl. The extinction coefficients of the dione in these solvent mixtures were 49.5 ± 0.1, 49.8 ± 0.6, and 49.3 ± 0.3, respectively. The extinction coefficients of 5α-androstan-3-one and 5α-androstan-17-one in 4:1 (v/v) dioxane–water were 24.2 and 24.7, respectively. These measurements indicate that, under the reaction conditions employed, ketal hydrolysis is complete and irreversible and is not complicated by hemiketal formation and that a linear relationship exists between optical density at 280 mμ and ketone concentration.

C. Equilibria Involving Steroid Cyclic Ketal Formation. Equilibrium constants were determined by equilibrating mixtures of dione, glycol, and catalyst in 1,2-dimethoxyethane (glyme)[17] at 50°.

For each equilibrium run, the initial amounts of dione, glycol, and *p*-toluenesulfonic acid monohydrate were weighed into 25-ml volumetric flasks. The mixtures were diluted to the mark with glyme which had been purified by repeated distillation from lithium aluminum hydride under vacuum. Aliquots of these mixtures were introduced into 2-ml glass vials by means of a hypodermic syringe and the vials were gently flushed with nitrogen gas, frozen

(13) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath, New York, N. Y., 1941, p 363.

(14) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740, 746 (1940), reports a mp of 132–134° for 5α-androstane-3,17-dione.

(15) R. H. Shapiro, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2837 (1964).

(16) The *p*-dioxane was purified as described in L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath, New York, N. Y., 1941, p 369.

(17) *p*-Dioxane could not be used as a solvent in these reactions as it partially decomposed under the reaction conditions into ethylene glycol, which competed with the glycol under study for ketalization of the dione.

in liquid nitrogen, and sealed. The sealed vials were placed in amber bottles which were placed in a water bath maintained at 50 ± 1°. At least three runs were conducted with the dione and a given glycol, each run representing a different ratio of initial glycol to dione concentration. Periodically, samples of the equilibrium mixtures were removed and quenched by the addition of several drops of triethylamine. The samples were then analyzed by glpc (see below) and relatively constant analytical values for successive samples were taken as an indication that equilibrium had been attained.

Model 15 and series 5000 Barber–Colman gas chromatography units equipped with Sr 90 detectors and a Packard Model 7503 dual-column gas chromatograph equipped with tritium detectors were used in this investigation. The carrier gas in all cases was argon.

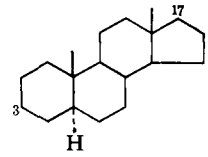
Anakrome[18] was the solid support used for the preparation of the chromatographic columns and was coated with the liquid phase by the filtration technique.[19] Liquid phases used included NGS (neopentyl glycol succinate),[18] QF-1 (fluorosilicate polymer),[18] SE-30 (silicon polymer),[18] and JXR (silicon polymer).[20]

Each sample was injected on the glpc column three to four times and each component was quantitated by comparison of its average peak height with those of standard solutions analyzed under the same conditions. The standard solutions were injected several times during each analysis and a good linear relationship between peak height and the amount of material injected was obtained. Those compounds which gave short, broad peaks were quantitated by comparison of their average peak areas with those of standard compounds.[21]

Results and Discussion

A. Hydrolysis of Steroid Cyclic Ketals. Examination of the kinetic data given in Table II indicates that several conclusions may be drawn concerning the acid

Table II. Relative Hydrolysis Rates of 5α-Androstane Cyclic Ketals[a]



5α-androstane

Glycol	3-Ketal	17-Ketal	3-Ketal 17-one	17-Ketal 3-one
Ethylene glycol	1.00[b]	1.64	1.06	1.51
1,3-Propanediol	14.5	40.5	13.8	48.3
2,2-Dimethyl-1,3-propanediol	1.52	6.90	1.26	5.24
2,2-Diethyl-1,3-propanediol	0.75	2.63	0.47	2.09

[a] These values represent the average of at least three kinetic runs with each ketal. The replicate determinations gave values within 3–5% of the mean: solvent = 4:1 (v/v) dioxane–water; temperature = 37 ± 0.15°; acid concentration = 0.02 *N* HCl. [b] This ketal was taken as a standard with a relative rate of 1.00. The observed average rate constant for this ketal was 1.0×10^{-2} min^{-1}.

hydrolysis of cyclic ketals of the 5α-androstane series: (a) the ketals derived from the cyclopentanone portion of the steroid (17-ketals) hydrolyze at a considerably faster rate than do the corresponding ketals derived from the cyclohexanone portion (3-ketals); (b) the ketals derived from ethylene glycol are much more stable toward acid hydrolysis than are the corresponding ketals derived from 1,3-propanediol; and (c) *gem*-dialkyl substitution increases the hydrolytic stability of the ketals derived from the 1,3-propanediols to the point that, in the case of 2,2-diethyl-1,3-propanediol, the resulting ketals hydrolyze at rates comparable to those of the ketals derived from ethylene glycol. These results are in agreement with those previously obtained[12] with the corresponding ketals of cyclopentanone, cyclohexanone, and 2-methylcyclopentanone.

The increased rates of hydrolysis of the ketals derived from the cyclopentanone portion of the steroid relative to those of the ketals derived from the cyclohexanone portion are in agreement with the generalization that, in in those reactions of cyclic systems which involve a change in the coordination number of carbon from four to three, the reaction will proceed faster for a cyclopentane derivative than for a cyclohexane derivative.[22] Since the rate-determining step in ketal hydrolysis involves such a change,[23] one would expect the 17-ketals to be hydrolyzed more rapidly than the 3-ketals. These rate differences are further illustrated by the data in Table III.

Table III. Relatives Rates of Hydrolysis of 5α-Androstane 3- and 17-Cyclic Ketals

Glycol	k_{17}/k_3[a] 17-Ketal/3-ketal	k_{17}/k_3[a] 17-Ketal 3-one/3-ketal 17-one
Ethylene glycol	1.64	1.42
1,3-Propanediol	2.80	3.50
2,2-Dimethyl-1,3-propanediol	4.48	4.16
2,2-Diethyl-1,3-propanediol	3.51	4.45

[a] k_{17} = rate constant for hydrolysis of the 17-ketal and k_3 = rate constant for hydrolysis of the 3-ketal.

The observed increased rates of hydrolysis of the ketals derived from 1,3-propanediol relative to those derived from ethylene glycol are in agreement with many other experimental examples which have led to the generalization that, in their reactions with polyhydric alcohols, aldehydes tend to form 1,3-dioxanes while ketones tend to form 1,3-dioxolanes.[24] In the present investigation, the ketals derived from 1,3-propanediol hydrolyzed from 13 to 32 times faster than those derived from ethylene glycol.

Reactions involving cyclic compounds and their open-chain precursors exhibit large substituent effects. Such effects are particularly great in the case of geminal substitution (the *gem* or *gem*-dialkyl effect).[25] These effects have been noted in the formation and/or hydrolysis of cyclic anhydrides,[26] lactones,[27] epoxides,[28] cyclic amines,[29] and cyclic ketals.[12] The effect of *gem*-diakyl substitution on the reactivity of steroid cyclic ketals toward acid hydrolysis, as illustrated by the data in Table IV, provides another example of the *gem*-di-

(18) Anakrome ABS (acid washed, base washed, and silinized) was obtained from Analabs Inc., Hamden, Conn.

(19) E. C. Horning, E. A. Mascatelli, and C. C. Sweely, *Chem. Ind.* (London), 751 (1959).

(20) Applied Science Labs. Inc., State College, Pa.

(21) Peak areas were calculated by the method of J. C. Bartlett and P. M. Smith, *Can. J. Chem.*, 38, 2057 (1960).

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(26) K. Auwers and V. Meyer, *Ber.*, 23, 101 (1890); T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, 87, 4838 (1965).

(27) R. T. Arnold and K. L. Lindsay, *ibid.*, 75, 1048 (1953).

(28) L. Smith, *Z. Phys. Chem.*, 156A, 135 (1933).

(29) R. F. Brown and N. Von Gulick, *J. Org. Chem.*, 21, 1046 (1956).

Table IV. Relative Hydrolysis Rates of 5α-Androstane Cyclic Ketals[a]

Glycol	3-Ketal	17-Ketal	3-Ketal 17-one	17-Ketal 3-one
1,3-Propanediol	1.00	1.00	1.00	1.00
2,2-Dimethyl-1,3-propanediol	0.10	0.17	0.09	0.11
2,2-Diethyl-1,3-propanediol	0.05	0.06	0.03	0.04

[a] In each series, the unsubstituted ketal is taken as a standard with a relative rate of 1.00. The observed rate constants for the 3-ketal, 17-ketal, 3-ketal 17-one, and 17-ketal 3-one were 0.145, 0.405, 0.138, and 0.483 min^{-1}, respectively: solvent = 4:1 (v/v) dioxane–water; temperature = 37 ± 0.15°; acid concentration = 0.02 *N* HCl.

Table V. Equilibrium Constants for Ketalization of 5α-Androstane-3,17-dione[a,b]

Glycol	K_6	K_5	K_6/K_5
Ethylene glycol	0.76	0.027	28
1,3-Propanediol	0.03	...	...
2,2-Dimethyl-1,3-propanediol	0.45	0.004	113
2,2-Diethyl-1,3-propanediol	0.57	0.002	285

[a] Solvent = 1,2-dimethoxyethane, temperature = 50 ± 1°, catalyst = *p*-toluenesulfonic acid monohydrate. [b] These values represent the average of four runs with each glycol, each run representing a different ratio of initial glycol to dione concentrations. The replicate determinations gave values within *ca.* 10% of the mean.

alkyl effect. In particular, the advantage to be gained by the use of ethyl rather than methyl groups is to be seen. Thus, the ketals derived from 1,3-propanediol are from 16 to 33 times as reactive as those derived from 2,2-diethyl-1,3-propanediol but only about 10 times as reactive as those derived from 2,2-dimethyl-1,3-propanediol. The stabilizing influence of the *gem*-dialkyl groups is such that, in the case of 2,2-diethyl-1,3-propanediol, the resulting ketals possess hydrolytic stabilities comparable, or slightly superior, to those of the corresponding ethylene cyclic ketals.

The observed decrease in hydrolysis rates upon *gem*-dialkyl substitution in the 1,3-diol moiety is in agreement with data obtained from a study of the hydrolytic stabilities of the cyclic ketals of cyclohexanone, cyclopentanone, and 2-methylcyclopentanone derived from 1,3-propanediol and several 2,2-dialkyl-1,3-propanediols.[12] In this study,[12] 2,2-diisopropyl-1,3-propanediol was shown to yield cyclic ketals which were more stable toward acid hydrolysis than any of the other ketals studied.

B. Equilibria Involving Steroid Cyclic Ketal Formation. A method of presenting the equilibrium data which clearly illustrate the differential abilities of the glycols studied to ketalize 5α-androstane-3,17-dione selectively at the 3 or 17 positions involves definition of two equilibrium ketalization constants

$$K_6 = \frac{(\text{3-ketal})(H_2O)}{(\text{3-ketone})(\text{glycol})} = \frac{X(W + X + Y)}{(100 - X)(G - X - Y)}$$

$$K_5 = \frac{(\text{17-ketal})(H_2O)}{(\text{17-ketone})(\text{glycol})} = \frac{Y(W + X + Y)}{(100 - Y)(G - X - Y)}$$

where concentrations are in molar per cent and K_6 = equilibrium constant for ketalization of the cyclohexanone portion of the dione; K_5 = equilibrium constant for ketalization of the cyclopentanone portion of the dione; X = mole per cent of material ketalized at the 3 position (3-ketal 17-one + 3,17-bisketal); Y = mole per cent of material ketalized at the 17 position (17-ketal 3-one + 3,17-bisketal); $100 - X$ = mole per cent of material not ketalized at the 3 position (17-ketal 3-one + 3,17-dione); $100 - Y$ = mole per cent of material not ketalized at the 17 position (3-ketal 17-one + 3,17-dione); W = initial water concentration; $(W + X + Y)$ = equilibrium water concentration; G = initial glycol concentration; and $G - X - Y$ = equilibrium glycol concentration. The values of K_6 and K_5 for the ketalization of 5α-androstane-3,17-dione with the diols studied are given in Table V.

The equilibrium data indicate that the stabilities of the cyclic ketals derived from the cyclohexanone portion of the dione (3-ketals) are much greater than those of the corresponding ketals derived from the cyclopentanone portion (17-ketals). The data are in agreement with the generalization that a double bond exocyclic to a five-membered ring is preferred relative to a double bond exocyclic to a six-membered ring.[22] Similar effects have been noted in the reaction of cyclohexanone and cyclopentanone with 2,2-dimethyl-1,3-propanediol[12] (K_6/K_5 = 10 at 30°) and anhydrous methanol[30] (K_6/K_5 = 30 at 10° and 15 at 25°).

The equilibrium data also indicate that the ratio K_6/K_5 varies considerably with the structure of the glycol involved and that this ratio is most favorable for monoketalization of the dione at the 3 position in the case of 2,2-diethyl-1,3-propanediol. Inspection of Dreiding models of 17-cyclic ketals of the 5α-androstane series indicates that the increase in the K_6/K_5 ratio may be largely due to steric interactions between the 2,2-dialkyl portion of the 17-ketal group and the C-12 hydrogens of the steroid nucleus and those of the adjacent angular methyl group.

The relative instability of steroid cyclic ketals derived from 1,3-propanediol as compared to those derived from ethylene glycol was discussed earlier in terms of the relative hydrolysis rates of these compounds and is emphasized by the data in Table V.

The effect of *gem*-dialkyl substitution in the diol upon steroid cyclic ketal formation is illustrated by the fact that, although K_6 in the case of ethylene glycol is 25 times that in the case of 1,3-propanediol, introduction of 2,2-dialkyl groups into 1,3-propanediol increases the stabilities of the resulting ketals so that K_6 is comparable to that for ethylene glycol. While the ketals derived from 2,2-diethyl-1,3-propanediol are the most stable, the greatest increase in stability occurs when the 2,2-dimethyl group is introduced into 1,3-propanediol.

The above kinetic and equilibrium data allow the following conclusions to be made concerning the formation and hydrolysis of cyclic ketals of the 5α-androstane series derived from ethylene glycol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, and 2,2-diethyl-1,3-propanediol: (a) the cyclic ketals derived from the cyclopentanone portion of 5α-androstane-3,17-dione (17-ketals) are less stable and are hydrolyzed more readily than are the corresponding ketals derived from the cyclohexanone portion (3-ketals); (b) the ketals derived

(30) J. P. Bell, D. G. Kubler, P. Sartwell, and R. G. Zepp, *J. Org. Chem.*, 30, 4284 (1965).

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.

(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).

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

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

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

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

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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(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.