STEREOSELECTIVE HYDROLYSIS OF 16α-HALO-17-KETO STEROIDS AND LONG-RANGE SUBSTITUTION EFFECTS ON THE HYDROLYSIS OF 16α-BROMO-17-KETONES AND 2α-BROMO-3-KETONES

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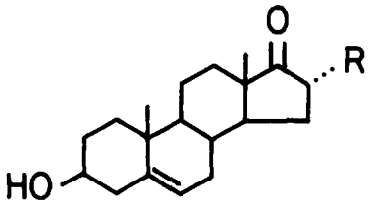
ABSTRACT

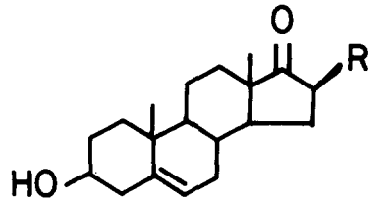
Epimerizations of 16α-chloro- (1a), bromo- (1b), and iodo-3β-hydroxy-5-androsten-17-one (1c) by a brief treatment with 0.2 equiv NaOH in aqueous pyridine reached equilibrium between 16α- and 16β-halo ketones. 16α-/16β-Halo ketone ratios at equilibrium were 1.5 for Cl, 1.25 for Br, and 1.0 for I. Kinetic analysis showed that compounds 1a-c were stereoselectively converted to the corresponding 16α-hydroxy derivative 3 by an S_N2 mechanism, in which the order of the apparent reactivity was Br > I > Cl. The hydrolysis of a number of 16α-bromo-17-ketones and 2α-bromo-3-ketones was carried out. The yields of the corresponding alcohols were found to depend on remote structural features in the steroids.

INTRODUCTION

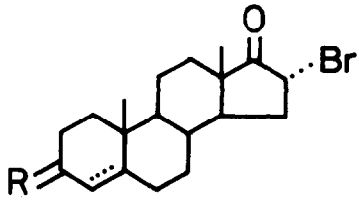
Hydrolysis of α-halo ketones is a fundamental reaction whose synthetic utility in steroid chemistry has been revolutionized in recent years by the discovery of controlled conditions for the use of a base in an aqueous solvent [1]. 16α-Bromo-17-oxo [1a-e] and 2α-bromo-3-oxo [1f] steroids can be stereoselectively converted in very high yield to the corresponding 16α-hydroxy-17-ketones and 2α-hydroxy-3-ketones by hydrolysis. Isotope labelling studies [1c,1f] demonstrate that the equilibration between the 16α- and 16β-bromo ketones or between the 2α- and 2β-bromo ketones precedes the displacement of bromine by the hydroxide ion, in which the true intermediate is the 16β-bromo or 2β-bromo isomer, and that the 16α-hydroxy or 2α-hydroxy derivatives



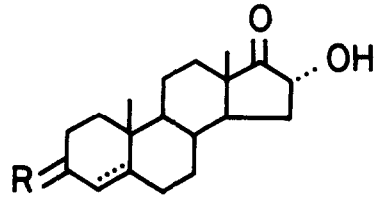
1a : R = Cl
b : R = Br
c : R = I
3 : R = OH
4 : R = H



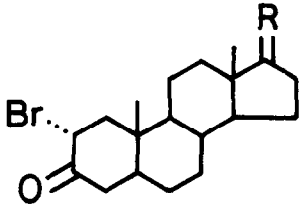
2a : R = Cl
b : R = Br
c : R = I



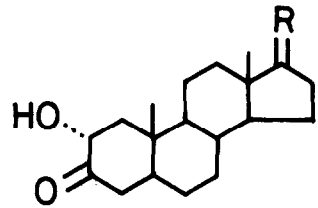
5 : R = H, 5α
6 : R = OH, 5α
7 : R = O, 5α
8 : R = O, Δ^4



9 : R = H, 5α
10 : R = OH, 5α
11 : R = O, 5α
12 : R = O, Δ^4



13 : R = O
14 : R = H
15 : R = OH
16 : R = $CH(CH_3)(CH_2)_3CH(CH_3)_2$



17 : R = O
18 : R = H
19 : R = OH
20 : R = $CH(CH_3)(CH_2)_3CH(CH_3)_2$

are formed by S_N2 displacement of the 16β-bromine or 2β-bromine.

In continuation of studies on the alkaline hydrolysis, it became of interest to know the relative reactivities of 16α-chlorides, -bromides and -iodides in an S_N2 mechanism, as well as the effect of remote structural features on the hydrolysis of 16α-bromo-17-ketone and 2α-bromo-3-ketones.

RESULTS AND DISCUSSION

The dynamic aspects of equilibrium between 16α- and 16β-halo-17-keto steroids 1 and 2 and of production of the corresponding 16α-hydroxy compound 3 were initially explored under the controlled alkaline hydrolysis conditions. Treatment of 16α-chloro- (1a), bromo- (1b) and iodo-3β-hydroxy-5-androsten-17-one (1c) with 0.12 equiv NaOH in 75% aqueous pyridine at room temperature caused the epimerization of the 16α-halo ketones (Table I). A 5-min reaction time was enough to give an approximate 1:1.5 equilibrium between 16-chloro ketones 1a and 2a and an approximate 1:1.25 equilibrium [1a,c] of the 16-bromo ketones 1b and 2b, in favor of the 16β-isomers 2a and 2b, respectively. The same reaction with 16α-iodo ketone 1c gave an almost 1:1 equilibrium between 16-iodo ketones 1c and 2c. Under the conditions, the formation of the 16α-hydroxy derivative 3 was negligible [2] and there was no significant difference in the epimerization rates between the halo ketones. The reason why the 16β-bromo ketone 2b is thermodynamically more stable than the 16α-isomer 1b has previously been discussed from the standpoint of the conformational differences of their D-rings [1c,2]. The 16β-chloro ketone 2a will similarly be more stable than the isomer 1a. It is noteworthy that the 16α-/16β-halo ketone ratios in the equi-

Table I. Epimerization of 16-Halo-17-ketones 1 with NaOH in Aqueous Pyridine[a)]

Time, min	16β-/16α-Halo-17-ketone ratio[b)]		
	Cl	Br	I
5	1.50	1.25	0.90
10	1.46	1.25	1.00
20	1.51	1.20	1.00

a) NaOH: 0.12 equiv. b) Substrates used were 1a for Cl, 1b for Br, and 1c for I. 16β-/16α-Halo ketone ratios were determined by HPLC analysis of the epimerization product.

librium between 16α- and 16β-halo ketones were in the sequence Cl > Br > I. This sequence can be interpreted in terms of a Van der Waals interaction between the halogen atom and the C-18 angular methyl group [3].

Reactions of 16α-chloro and 16α-iodo ketones 1a and 1c with 1.2 equiv NaOH under the controlled conditions gave the same product 3 in good yields (Table II). This appears to be the first example of the successful stereoselective hydrolysis of α-chloro and α-iodo keto

Table II. Hydrolysis of 16α-Halo-17-ketones 1 with NaOH in Aqueous Pyridine

Conditions		Yield of 3, %[a)]		
NaOH, eq	Time, min	Cl	Br	I
0.2	10	0.3	30	19 (6)[b)]
0.4	10	15	68	42 (11)
1.2	60	65	99	60 (20)

a) Substrates used are same as in Table I. Yield was obtained by HPLC analysis. b) Yield of 4 was presented in parentheses.

steroids with NaOH. In the latter experiment, the deiodinated product 4 was produced (20%) along with 3. Compound 4 may be reductively produced by the reaction of 1c with I^- released in the reaction medium during the displacement reaction. The experimental procedure selected for the hydrolysis rate measurements of 16α-halo ketones employed 0.2 and 0.4 equiv of NaOH to approximate pseudo-first-order rate conditions. The relative rates for the three halo ketones were Br > I > Cl. An increasing production of 16α-hydroxy derivative 3 in proportion to the amount of NaOH was observed in the halo ketones 1a-c (Table II), maintaining the remaining halo ketones in the same equilibrium between 16α- and 16β-halo ketones as shown in Table I. This shows that the

Table III. Hydrolysis of 2α-Bromo-3-ketones and 16α-Bromo-17-ketones

Structural change	Substrate	Product	Yield,%[a]	Relative yield
2α-Bromo-3-ketones[b]				
17-keto	13	17	32	1.5
17-H_2	14	18	31	1.5
17β-OH	15	19	29	1.4
17β-$CH(CH_3)(CH_2)_3$-$CH(CH_3)_2$	16	20	21	1.0
16α-Bromo-17-ketones[c]				
3-H_2	5	9	18	2.5
3β-OH	6	10	16	2.3
5-ene-3β-OH	1	3	15	2.2
3-keto	7	11	8.6	1.2
4-ene-3-keto	8	12	7.0	1.0

a) Yields were determined by HPLC analysis and presented as a mean value of duplicate experiments. b) NaOH, 0.5 equiv; solvent, 87% aqueous pyridine; reaction time, 20 min. The relative yield of the ketol was obtained, compared to that with 16. c) NaOH, 0.25 equiv; solvent, 75% aqueous pyridine; reaction time, 20 min. The relative rate of the reaction was obtained, compared to that with 8.

hydrolysis of 16-chloro and 16-iodo ketones proceeds by the same mechanism (S_N2 displacement of 16β-chlorine and -iodine by hydroxide ion) as that involved in the hydrolysis of 16-bromo ketones [1c]. It is well established that the relative reactivities of corresponding aliphatic chlorides, bromides and iodides by the S_N2 mechanism are unambiguously in the sequence I > Br > Cl [4]. The apparent low reactivity of 1c would be caused by the deiodination reaction.

In order to determine long-range effects in the controlled hydrolysis of α-halo keto steroids, a series of 2α-bromo-3-ketones or 16α-bromo-17-ketones was subjected to the reaction, in which the corresponding 2α-alcohols or 16α-alcohols are the sole product. The yields are given in Table III. They are listed relative to the corresponding yield for the cholestane derivative 16 or the 4-ene-3-keto derivative 8. The 2α-bromo-3-ketones 13 (17-keto), 14 (17-H_2), and 15 (17β-OH) were converted to the corresponding 2α-hydroxy derivatives 17, 18, and 19 almost in the same yields. The yield of hydrolysis of the 2α-bromo cholestane derivative 16 was lower than the others. On the other hand, low relative yields of the 16α-hydroxy ketones 11 and 12 were obtained by the hydrolysis of the corresponding 16-bromo ketones 7 and 8 having a 3-keto group; these yields were approximately one-half of those of the 3β-hydroxy derivatives 3 and 10 and of the 3-deoxy derivative 9.

Although exact kinetic data were not obtained in this study, the present results show that the conversion rates depend on structural features of the steroids at points remote from the site of the reaction. The conformational transmission of distortion [5] would be in operation in the hydrolysis reaction under the controlled condition, similarly as in the case previously reported [6,7].

EXPERIMENTAL

General Methods. Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR 400 spectrometer as KBr pellets. ^{1}H-NMR spectra were obtained with a JEOL PMX 60 spectrometer using tetramethylsilane as an internal standard. Optical rotation was taken with a JASCO DIP-140 digital polarimeter. High-performance liquid chromatography (HPLC) was carried out on a Waters ALC/PGC 244 liquid chromatograph equipped with a U6K injector and a differential refractometer detector.

16α-Halo-17-ketones 1a-c. Compounds 1a-c were synthesized according to the previously reported methods [1,8,9].

16β-Halo-17-ketones 2a-c. Preparative HPLC of the reaction mixtures of 1a-c and 2a-c obtained from the epimerization of 1a-c with 0.2 equiv NaOH in 75% aqueous pyridine gave 2 in 20-40% yields. HPLC conditions: column, Erma ERC-ODS (10 cm x 0.6 i.d. cm); mobile phase, MeOH/H_2O= 7/3 or 6/4, v/v (solvent 1 or 2); flow rate 2.0 ml/min. Retention time: 1a and 2a, 8.2 and 10.5 min (solvent 2); 1b and 2b, 4.1 and 5.2 min (solvent 1); 1c and 2c, 4.8 and 6.2 min (solvent 1).

16β-Chloro-3β-hydroxy-5-androsten-17-one 2a. mp 155-156 °C; IR (KBr) 3275 and 1748 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (6H, s, 18- and 19-CH_3), 3.53 (1H, br m, 3α-H), 4.00 (1H, t, J=8 Hz, 16α-H), 5.38 (1H, m, 6-H); $[\alpha]_D$ + 33° (c=0.38, $CHCl_3$). Anal. Calcd. for $C_{19}H_{27}O_2Cl$: C, 70.68; H, 8.43. Found: C, 70.85; H, 8.51.

Epimerization of the 16α-Halo-17-ketones 1a-c in NaOH-Aqueous Pyridine. To a solution of the 16α-halo-17-ketones 1a-c (0.22 mmol) in 75% aqueous pyridine (4.2 ml) was added 0.26 ml of 0.1N NaOH solution, and the mixture was allowed to stand at room temperature for an appropriate period. The mixture was poured into a 5% HCl solution and then extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ and water, and dried with Na_2SO_4. After evaporation of the solvent, the residue was submitted to HPLC analysis.

16α-Bromo-17-ketone. The bromo ketones were synthesized essentially according to our previous report [1c].

2α-Bromo-3-ketone. The bromo ketones were obtained according to the previously reported methods [10-12].

Hydrolysis of a 16α-Bromo-17-ketone and of a 2α-Bromo-3-ketone. Solutions of the 16α-bromo ketone (0.27 mmol) in 75% aqueous pyridine (5.6 ml) and 2α-bromo ketone (0.14 mmol) in 87% aqueous pyridine (23 ml) containing various amounts of NaOH were allowed to stand at room temperature for 20 min. After the same workup as above mentioned, the 16α-hydroxy-17-ketone and 2α-hydroxy-3-ketone produced from the corresponding 16α- and 2α-bromo ketones were analyzed by HPLC. HPLC conditions: column, μ-Bondapak C_{18} (30 cm x 0.4 i.d. cm; solvent flow rate, 1.5 ml/min) for the 16α-bromo ketone experiment and ERS-ODS (10 cm x 0.6 i.d. cm)(solvent flow rate, 2 ml/min) for the 2α-bromo ketone experi-

ment. Retention time: 3.5 min for 9 [MeOH/H_2O=9/1, v/v (solvent 3)] ; 6.0 min for 10 (solvent 2); 5.7 min for 11 (solvent 2); 4.4 min for 12 (solvent 2); 5.4 min for 3 (solvent 2); 3.6 min for 17 (solvent 2); 2.5 min for 18 (solvent 3); 4.4 min for 19 (solvent 2); 3.0 min for 20 (MeOH).

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