CONTROLLED ALKALINE HYDROLYSIS OF STEROIDAL α-BROMOKETONES: NEW CONDITIONS AND SYNTHESIS OF 2α-HYDROXY-3-ONES

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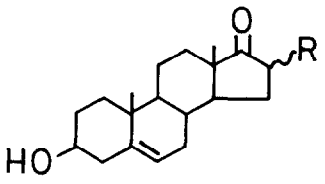
ABSTRACT

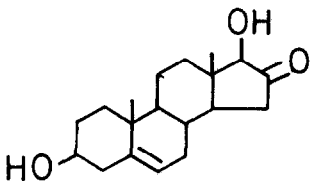
Controlled alkaline hydrolysis of 16α-bromo-17-keto steroids 1, 5 and 7 with potassium carbonate and tetra-n-butylammonium hydroxide (n-Bu_4NOH) and synthesis of 2α-hydroxy-3-ones 11, 13 and 16 by the controlled hydrolysis of the corresponding 2α-bromo-3-ones 9, 12 and 15 are described. Treatment of the bromoketones 1, 5 and 7 with potassium carbonate in aqueous acetone or with n-Bu_4NOH in aqueous dimethylformamide (DMF) gave 16α-hydroxy-17-ones 3, 6 and 8 in 85-90% yield, respectively. 2α-Hydroxy-3-ones 11, 13 and 16 were obtained by hydrolysis of the corresponding bromoketones 9, 12 and 15 in high yields using the above conditions or sodium hydroxide in pyridine or DMF, respectively. Deuterium labeling experiments suggested that equilibration between the 2α-bromoketone 9 and the 2β-bromo isomer 10 precedes the formation of the ketol 11 in which the true intermediate might be the 2β-isomer 10. However, rearranged androstane derivatives, 3β-hydroxy-2-ones 18 and 20, were stereoselectively obtained by treatment of the bromoketones 12 and 15 with an excess amount of sodium hydroxide.

INTRODUCTION

Hydrolysis of α-bromoketones is one of fundamental organic reactions whose synthetic utility in steroid chemistry has been revolutionized in recent years by the discovery of the controlled conditions using sodium hydroxide in aqueous pyridine [1] or dimethylformamide (DMF) [2]. 16α-Hydroxylated C_{18} and C_{19} steroids [2,3] and their 3-sulfates [1,4] could be synthesized by the controlled stereoselective hydrolysis of the corresponding 16-bromo-17-ones in one step in very high yields. Estriol 16-glucuronide was also efficiently obtained by a short step synthesis involving the hydrolytic method as a key reaction [5].



1 R =···Br
2 R =—Br
3 R =···OH



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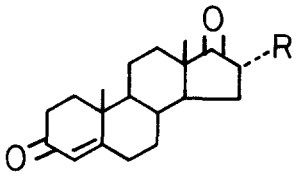
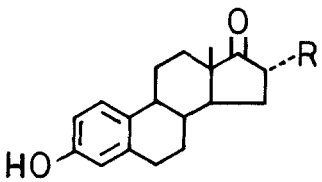
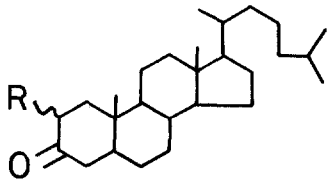


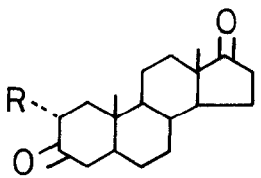
5 R = Br
6 R = OH



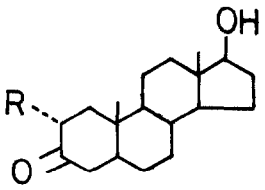
7 R = Br
8 R = OH



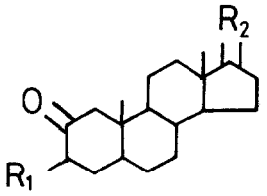
9 R =···Br
10 R =—Br
11 R =···OH

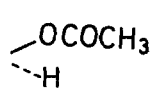


12 R = Br
13 R = OH
14 R = $OCOCH_3$



15 R = Br
16 R = OH
17 R = $OCOCH_3$



18 R_1 = OH , R_2 = O
19 R_1 = $OCOCH_3$, R_2 = O
20 R_1 = OH , R_2 = 
21 R_1 = $OCOCH_3$, R_2 = 

The reaction of 2α-bromo-3-keto steroids with a nucleophile, methoxide [6] or acetoxy [7-9] ion, did not afford the 2α-hydroxy-3-one derivatives in high yields since Favorskii or ketol rearrangement is involved in the reaction. The previous observations led to a general belief that it is impossible to isolate the corresponding ketols by hydrolysis of 2α-bromo-3-ones because of the instantaneous rearrangements.

We report new conditions of the controlled alkaline hydrolysis with potassium carbonate or tetra-n-butylammonium hydroxide (n-Bu_4NOH). A new utilization of the hydrolytic method in syntheses of 2α-hydroxy-3-ones from the corresponding bromoketones and its reaction mechanism are also described.

RESULTS AND DISCUSSION

Alkaline hydrolysis of 16α-bromo-3β-hydroxy-5-androsten-17-one (1) with bases, potassium carbonate, potassium bicarbonate and n-Bu_4NOH, other than sodium hydroxide was initially explored in an aqueous solvent, acetone or DMF. Dynamic aspects of epimerization and hydrolysis of the bromoketone 1 are shown in Table I. Treatment of the bromoketone 1 with 1 mole equivalent of potassium carbonate in aqueous acetone (conditions A and B) gave an approximate 1:1.4 equilibrium between the bromoketone 1 and its 16β-bromo isomer 2 in favor of the 16β-isomer 2 with 55-72% yield of 16α-hydroxy-17-one 3 and 2-3% yield of the rearranged product, 17β-hydroxy-16-one 4, while an approximate 1:3 equilibration between the bromoketones with 68-82% yield of the ketol 3 was observed using 1.2 mole equivalent of n-Bu_4NOH in aqueous DMF (conditions F and G). The marked difference in the equilibration between the bromoketones might be due to a stabilization of the less stable 16β-isomer 2 [10] in the latter

Table I. Epimerization of the 16α-Bromo-17-one 1 and Formation of the 16α-Hydroxy-17-one 3 with a Base in an Aqueous Solvent.

Conditions			Relative Amount of Product (%)[a]			
	Base (mol equiv)	Time (hr)	1	2	3	4
1) K_2CO_3-50% aqueous acetone[b]						
A	1	0.5	18	25	55	2
B	1	1.0	6	9	72	3
C	1	1.5	0	0	96	4
2) $KHCO_3$-50% aqueous acetone[b]						
D	2	4	6	8	64	22
E	4	3	0	0	74	26
3) n-Bu_4NOH-75% aqueous DMF[c]						
F	1.2	0.17	8	24	68	0
G	1.2	0.5	4	14	82	0
H	2.5	0.17	0	0	98	2

a) Relative amount of product was obtained by peak areas corresponding to both C-16 proton and C-18 angular methyl by ^{1}H-NMR spectra of the reaction mixtures without isolation.
b) The reaction mixture was heated under reflux.
c) The reaction mixture was allowed to stand at room temperature.

conditions. The results demonstrate that the equilibration between the bromoketones precedes the formation of the ketol 3 in which the true intermediate is the 16β-isomer 2 and that the ketol is formed by the direct S_N2 displacement of bromine with hydroxide ion in analogy with the previous reports [1,2]. Although a small amount (2-4%) of the rearranged ketol 4 was produced by treatment of the bromoketone 1 with potassium carbonate (condition C) or n-Bu_4NOH (condition H), the ketol 3 could be finally isolated in 85-90% yield by crystallization of the crude products. On the other hand, the potassium bicarbonate-acetone system caused rearrangement to a considerable extent. This may be due to exposure of the product 3 to the alkaline condition for a long time.

16α-Hydroxy-4-androstene-3,17-dione (6) and 3,16α-dihydroxy-

1,3,5(10)-estratrien-17-one (8) were obtained in a high yield from the corresponding bromoketones 5 and 7 using potassium carbonate or n-Bu_4NOH as a base, respectively. The yields are comparable to those previously reported [2,3]. The two systems have the advantage over the sodium hydroxide-pyridine system [1,2] in shorter reaction time, and the 16α-hydroxy-17-one product can be easily isolated using acetone as a solvent.

Evans *et al.* [6] reported the formation of 2α-hydroxy-5α-cholestan-3-one (11) as a minor product along with acidic products by treatment of the corresponding 2α-bromo-3-one 9 with sodium methoxide. Compound 11 has also been synthesized by the acyloin condensation of the 2,3-seco-diester [11]. Treatment of the bromoketone 9 with potassium acetate in acetic acid [7] or tetramethylammonium acetate [8] in acetone has been reported to give a complex of 2α- and 4α-acetoxy-5α-cholestan-3-ones, or of 2α-acetoxy-5α-cholestan-3-one and its rearranged product, 3β-acetoxy-5α-cholestan-2-one, respectively.

In order to develop a new utilization of the controlled reaction for practical and inexpensive synthesis of other steroidal ketols, the hydrolysis of 2α-bromo-3-keto steroids was examined. When the 2α-bromo-3-one 9 [12] was submitted to hydrolysis using sodium hydroxide in DMF or pyridine, potassium carbonate in acetone, or n-Bu_4NOH in DMF, 2α-hydroxy-3-one 11 was formed in very good yields without the formation of other ketols and acidic products (Table II). On the other hand, when ethanol was used as a solvent in the reaction, acidic products from the Favorskii rearrangement resulted in a low yield of the ketol 11. In these experiments, a low water content of the solvent was employed because of the solubility of compound 9. The choice of solvent in the hydrolysis is important, as pointed out in the previous reports [1,2].

Table II, Hydrolysis of the 2α-Bromo-3-one 9 with a Base in an Aqueous Solvent.

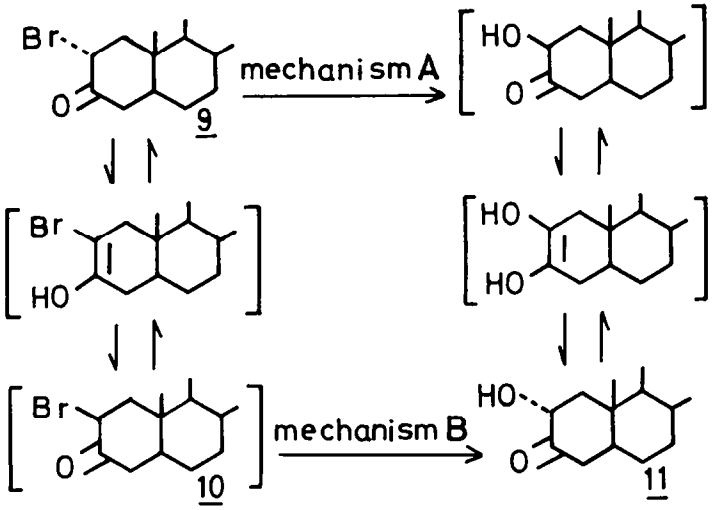
	Solvent	Conditions: Base (mol equiv)	Conditions: Time (min)	2α-Hydroxy-3-one 11: Isolated Yield (%)
I	83% pyridine	NaOH, 4	30	83
J	93% DMF	NaOH, 4	30	78
K	93% EtOH	NaOH, 4	30	41 (15)[a]
L	93% DMF	n-Bu_4NOH, 1.2	30	88
M	83% acetone	K_2CO_3, 1	30	86
N	83% acetone (17% D_2O)	K_2CO_3, 1	10	45 (42)[b]

a) The amount of acidic products.
b) The amount of the bromoketone 9 recovered.

2α-Hydroxy-5α-androstane-3,17-dione (13) and 2α,17β-dihydroxy-5α-androstan-3-one (16) were also obtained by treatment of the bromoketones 12 [13] and 15 [14] with 1.2 equivalent of sodium hydroxide in DMF. On the other hand, when 2 equivalents of the base was used in the reaction, 3β-hydroxy-2-ones 18 and 20, the rearranged products of the corresponding 2α-hydroxy-3-ones 13 and 16, respectively, were stereoselectively obtained in high yields. The structures of the ketols 11, 13, 16, 18 and 20 were identified by the IR and NMR spectra [15]. The fact that the rearranged cholestane derivative was not produced by the use of an excess amount of base (Table II) suggests that a conformational transmission of distortion through rings B, C and D might be in operation.

The mechanism of the stereoselective formation of the 2α-hydroxy-3-ones was then explored. When deuterium oxide (99.5 atom%) was used in the reaction mixture containing compound 9 as a substrate (condition N), a different degree of the d-labeling at the C-2 position between the recovered substrate (51%) and the 2α-hydroxy-3-one 11 (99%) was observed by ^{1}H-NMR analysis. The results show that the epimerization of the 2α-

Scheme I



bromo isomer 9 to the 2β-isomer 10 which d-content at C-2 should be more than 99%, occurs in the reaction, although compound 10 could not be detected in the reaction mixture. Considering the thermodynamical unstability and the reactivity of 2β-isomer 10, which has an axial bromine at C-2, the ketol 11 is apparently formed through steric and stereoelectronic effects by mechanism B (Scheme I), where the equilibration between the bromoketones 9 and 10 precedes the formation of the ketol 11 in which the true intermediate is the 2β-isomer 10 but not the 2α-isomer 9. The mechanism is in analogy with that of the hydrolysis of 16α-bromo-17-ones. Furthermore, when the ketol 11 was treated with deuterium oxide under condition N, the d-labeling at the C-2 position of the recovered ketol 11 was only 7% by MS analysis. The result eliminates mechanism A, where the 2α-isomer 9 is the true intermediate and the epimerization of the bromoketone is not a prerequisite.

EXPERIMENTAL

General methods. Melting points were measured on Yanagimoto melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu 400 spectrophotometer in KBr pellets. ^{1}H-NMR spectra were obtained with JEOL PMX 60 spectrometer at 60 MHz using tetramethylsilane as an internal standard.

Epimerization of the bromoketone 1 and formation of the 16α-hydroxy-17-one 3. To a solution of the bromoketone 1 [16] (0.20 mmol) in 50% aqueous acetone (25 ml) or 75% aqueous DMF (4 ml) was added a base (K_2CO_3, $KHCO_3$ or n-Bu_4NOH). The reaction mixture was allowed to stand at room temperature (DMF) or heated under reflux (acetone) for an appropriate time and then poured into 1% HCl solution and extracted with AcOEt (30 ml x 2). The organic layer was washed with 5% $NaHCO_3$ solution and H_2O and dried (Na_2SO_4). After evaporation of the solvent the residue obtained (55-60 mg) was submitted to ^{1}H-NMR analysis. ^{1}H-NMR ($CDCl_3$): 1 δ 0.90 (3H, s, 18-CH_3), 4.57 (1H, m, 16β-H); 2 δ 1.09 (3H, s, 18-CH_3), 4.14 (1H, t, J= 8 Hz, 16α-H); 3 δ 0.96 (3H, s, 18-CH_3), 4.37 (1H, m, 16β-H).

3β,16α-Dihydroxy-5-androsten-17-one (3). The residues obtained under conditions C and H were recrystallized from MeOH to give compound 3 (53 mg, 85% and 56 mg, 90%), respectively, as colorless needles, mp 189-190°C (lit. [16] 188-190°C).

16α-Hydroxy-4-androstene-3,17-dione (6). Compound 5 [17] was hydrolyzed by same conditions as above. Crystallization of the crude products from acetone gave compound 6 (condition C 46 mg, 77%; condition H 51 mg, 85%), respectively, as colorless plates, mp 188-190°C (lit. [16] 188-191°C). ^{1}H-NMR ($CDCl_3$): δ 1.00 (3H, s, 18-CH_3), 1.21 (3H, s, 19-CH_3), 4.36 (1H, m, 16β-H), 5.72 (1H, s, 4-H).

3,16α-Dihydroxy-1,3,5(10)-estratrien-17-one (8). The hydrolyzed residues of compound 7 [4] obtained under same conditions as above were recrystallized from MeOH to give compound 8 (condition C 49 mg, 86%; condition H 51 mg, 85%), respectively, as colorless needles, mp 204-206°C (lit. [4] 203-206°C). ^{1}H-NMR ($CDCl_3$): δ 0.97 (3H, s, 18-CH_3), 4.40 (1H, m, 16β-H), 6.51-7.20 (3H, m, aromatic protons).

Hydrolysis of the 2α-bromoketone 9. A) To a solution of the bromoketone 9 (50 mg, 0.107 mmol) in 45 ml of an appropriate solvent was added 0.42 ml of 1N NaOH solution or 1.2 equivalent of n-Bu_4NOH and the mixture allowed to stand at room temperature for 30 min. The mixture was poured into 1% HCl solution and then extracted with AcOEt (50 ml x 2). The organic layer was washed with 5% $NaHCO_3$ solution and H_2O and dried (Na_2SO_4). After evaporation of the solvent the residue (40-43 mg) was obtained.

B) To a solution of compound 9 (50 mg, 0.107 mmol) in 83% aqueous acetone (30 ml) was added K_2CO_3 (14 mg) and the reaction mixture was heated under reflux for 30 min. After the same work-up as above the residue (44 mg) was obtained.

2α-Hydroxy-5α-cholestan-3-one (11). Crystallization of the residue obtained above from acetone afforded compound 11 (78-88%) as colorless needles, mp 138-141°C (lit.[9] 126.5-128.5°C). ^{1}H-NMR ($CDCl_3$): δ 0.68 (3H, s, 18-CH_3), 1.10 (3H, s, 19-CH_3), 4.23 (1H, dd, J=7 and 14 Hz, 2β-H). IR (KBr): ν_{max} 3450 (OH), 1722 (C=O).

Compound 11 was treated by the procedure of Sheehan and Erman [11] with acetic anhydride in pyridiene to give the 2α-acetate (68%) as colorless needles (from acetone-n-hexane), mp 127-129°C (lit. [9] 124.5-125.2°C). ^{1}H-NMR ($CDCl_3$): δ 0.67 (3H, s, 18-CH_3), 1.12 (3H, s, 19-CH_3), 2.12 (3H, s, $OCOCH_3$), 5.35 (1H, dd, J=6 and 11 Hz, 2β-H). IR (KBr): ν_{max} 1750 and 1728 (C=O).

Hydrolysis of 2α-bromo-5α-androstan-3-ones. A) To a solution of the 2α-bromo-3-one 12 [13] or 15 [14] (0.27 mmol) in 83% aqueous DMF (16 ml) was added 0.32 or 0.54 ml of 1N NaOH solution and the mixture was allowed to stand at room temperature for 60 min. The residue (70-75 mg) was obtained by the same procedure as above.
B) The 2α-bromo-3-one 12 or 15 (0.27 mmol) was dissolved in 83% aqueous acetone (20 ml). To this solution was added 1 mol equivalent of K_2CO_3 and the mixture was heated under reflux for 30 min. The residue was obtained by the same procedure as above.

2α-Hydroxy-5α-androstane-3,17-dione (13). The residue obtained by method A using 0.32 ml of 1N NaOH solution and method B was recrystallized from acetone to give compound 13 (81 and 85%) as colorless needles, mp 169-172°C. ^{1}H-NMR ($CDCl_3$): δ 0.87 (3H, s, 18-CH_3), 1.12 (3H, s, 19-CH_3), 4.33 (1H, dd, J=7 and 12 Hz, 2β-H). IR (KBr): ν_{max} 3450 (OH), 1730 and 1715 (C=O).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27.
Found C, 75.11; H, 9.05.

2α-Acetoxy-5α-androstane-3,17-dione (14). Compound 13 (50 mg, 0.16 mmol) was acetylated by the usual method. Crystallization of the crude product from acetone gave compound 14 (77%) as colorless needles, mp 218-220°C. ^{1}H-NMR ($CDCl_3$): δ 0.90 (3H, s, 18-CH_3), 1.16 (3H, s, 18-CH_3), 2.13 (3H, s, $OCOCH_3$), 5.30 (1H, dd, J=7 and 14 Hz, 2β-H). IR (KBr): ν_{max} 1745, 1735 and 1723 (C=O).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73.
Found C, 72.55; H, 8.71.

2α,17β-Dihydroxy-5α-androstan-3-one (16). The residue obtained by method A using 0.32 ml of 1N NaOH solution and method B was recrystallized from acetone to give compound 16 (80 and 83%) as colorless needles, mp 170-172°C. ^{1}H-NMR ($CDCl_3$): δ 0.76 (3H, s, 18-CH_3), 1.13 (3H, s, 19-CH_3),3.63 (1H, t, J=8 Hz, 17α-H), 4.27 (1H, dd, J=8 and 14 Hz, 2β-H). IR (KBr): ν_{max} 3460 and 3340 (OH), 1715 (C=O).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87.
Found C, 74.40; H, 9.77.

2α,17α-Diacetoxy-5α-androstan-3-one (17). Compound 16 (50 mg, 0.16 mmol)

was acetylated by the usual method. Crystallization of the crude product from acetone gave compound 17 (89%) as colorless needles, mp 198–

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