chloride and 4.24 g (0.176 mol) of magnesium turnings in 100 mL of dry tetrahydrofuran. The reaction was initiated with a few crystals of iodine and the mixture allowed to react for 8 h at 60 °C. It was poured onto solid carbon dioxide, after which dilute hydrochloric acid was added. The aqueous layers were extracted with ether, and the combined extracts were evaporated to give a residue which was distilled at ca. 0.2 mm to give 18.2 g (69%) of a waxy solid.

The mixture of acids was converted to the methyl esters by means of diazomethane in ether. GC analysis on a 150-ft Apiezon L capillary column revealed two peaks in a 2:1 ratio: NMR δ 3.57 (s) and 3.52 (s), area ratio 37:63, respectively.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.18; H, 8.42.

Bromination of Tricyclo[3.2.1.0^{3,6}]octane-2-carboxylic Acid. A solution of 7.9 g (0.052 mol) of acid **11**, 9.5 g (0.059 mol) of bromine, and 0.224 mL (0.0025 mol) of phosphorus trichloride was heated for 17 h at 76 °C. Another 0.05 mL of PCl_3 was added, and the solution was heated for 24 h at 90–95 °C. The syrupy oil was triturated with pentane to yield 1.5 g of a tan solid, mp 130–140 °C. On crystallization from nitromethane the melting point was 152–155 °C.

Anal. Calcd for $C_9H_{11}O_2Br$: C, 46.77; H, 4.80; Br, 34.58. Found: C, 46.94; H. 4.85; Br, 34.53.

Treatment of the pentane filtrate with charcoal and reevaporation gave another 1.65 g of crystalline bromo acid. The oily residue was esterified with diazomethane and shown by GC (B) to contain only the methyl esters of **11** and the methyl esters of the bromo acids in a 60:40 ratio as determined by the ratio of the NMR peaks at δ 3.80 and 3.74.

Hydrogenolysis of Methyl Esters of 12. A mixture of the bromo esters (3.5 g, 0.0143 mol) and 4.7 g (0.072 mol) of granular zinc was stirred in 35 mL of glacial acetic acid at 40–50 °C for 40 h. The reaction mixture was poured into water and extracted with pentane. The dried extracts were evaporated, and the residue was distilled at 0.2 mm to yield 2.27 g (95%) of the esters of **11** as shown by GC (150-ft Apiezon L column), IR, and NMR comparisons.

Proof of Structure of 11. Preparation of 2-Acetylbicyclo[3.2.1.0^{3,6}]octane (13). A stirred solution of 2.0 g (0.013 mol) of **11** in 125 mL of anhydrous ether was treated dropwise with 16 mL of 1.67 M methyllithium solution over a period of 1.5 h. After an additional 0.5 h of vigorous stirring, the reaction was quenched with 25 mL of water. The aqueous layer was washed with ether, and the combined extracts were dried and evaporated to yield 2.0 g (100%) of an oil with a carbonyl absortpion at 5.90 nm and two closely spaced singlets in the NMR at δ 1.96 and 2.02 (relative area ca. 40:60). GC analysis (A or capillary) revealed one major peak (>96%).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.40. Found: C, 80.16; H, 9.70.

Oxidation of 13 with Trifluoroperacetic Acid. A solution of trifluoroperacetic acid was prepared by addition of 6.8 mL (0.041 mol) of trifluoroperacetic anhydride with cooling over 1 h to a solution of 1.04 mL (0.038 mol) of 90% hydrogen peroxide in 13.2 mL of methylene chloride. The resulting solution was stirred for 10 min and then added dropwise to a solution of 3.2 g (0.021 mol) of ketone **13** in a slurry of 40 mL of methylene chloride–potassium hydrogen phosphate (15.6 g, 0.11 mol). The resulting mixture was refluxed for 8 h and filtered to remove salts, and the filtrate was evaporated to give 3.5 g of crude product. GC analysis (A) revealed one major component (90%) which was isolated and shown by NMR to consist of a mixture of 2-*exo*- and 2-*endo*-tricyclo[3.2.1.0^{3,6}]octyl acetates[2] in a ratio of ca. 2:1. Lithium aluminum hydride reduction of the mixture gave a 2:1 mixture of 2-*exo*- and 2-*endo*-tricyclo[3.2.1.0^{3,6}]octanols as shown by NMR comparison of the area ratios of the carbinol protons at δ 3.7 and 4.1.[2]

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Registry No. 4, 73770-57-7; **4** *p*-nitrobenzoate ester, 73770-58-8; **5** (isomer 1), 73770-59-9; **5** (isomer 2), 73803-41-5; **6**, 73770-60-2; **6** *p*-nitrobenzoate ester, 73770-61-3; **7**, 73770-62-4; **8**, 73770-63-5; **9**, 73770-64-6; **11**, 25679-33-8; **11** methyl ester (isomer 1), 73770-65-7; **11** methyl ester (isomer 2), 73803-42-6; **12**, 73770-66-8; **12** methyl ester (isomer 1), 73770-67-9; **12** methyl ester (isomer 2), 73803-43-7; **13** (isomer 1), 73770-68-0; **13** (isomer 2), 73803-44-8; *endo*-2-methyl-*exo*-2-tricyclo[3.2.1.0^{3,6}]octanol, 73803-45-9; *endo*-2-methyl-*exo*-2-tricyclo[3.2.1.0^{3,6}]octanol acetate ester, 73770-69-1; *endo*-2-phenyl-*exo*-2-tricyclo[3.2.1.0^{3,6}]octanol, 73803-46-0; *exo*-2-chlorotricyclo[3.2.1.0^{3,6}]octane, 41564-23-2; *exo*-tricyclo[3.2.1.0^{3,6}]octan-2-ol, 6239-90-3; 2-*exo*-tricyclo[3.2.1.0^{3,6}]octyl acetate, 6239-95-8; 2-*endo*-tricyclo[3.2.1.0^{3,6}]octyl acetate, 73803-47-1; tricyclo[3.2.1.0^{3,6}]octan-2-one, 6239-87-8; 2-*endo*-tricyclo[3.2.1.0^{3,6}]octanol, 6239-89-0.

Acid- and Base-Catalyzed Isomerization of Androst-5-ene-3,17-dione and 17α-Ethynyl-17β-hydroxy-5-estren-3-one

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Isomerization of androst-5-ene-3,17-dione (**1**) to androst-4-ene-3,17-dione (**2**) and of 17α-ethynyl-17β-hydroxy-5-estren-3-one (**3**) to 17α-ethynyl-17β-hydroxy-4-estren-3-one (**4**) is kinetically general acid–base catalyzed; **1** is more reactive than **3**. Deuterium solvent kinetic isotope effects, $k(H_2O)/k(D_2O)$, of ca. 6 for tertiary amine catalyzed isomerization indicate rate-determining protonation of dienolate ions. The greater reactivity of **1** than **3**, catalyzed by tertiary amines, is probably due to a greater concentration of the **1** dienolate ion than of the **3** dienolate ion. Ethanolamine, but not tris(hydroxymethyl)aminomethane, catalyzes isomerization of **1** and **3** via Schiff-base formation. Curvilinear pseudo-first-order plots for isomerization of **1** and **3** catalyzed by DCl/D_2O indicate that partitioning of dienols is kinetically important.

Two kinetics studies of base-catalyzed isomerization of Δ^5-3-keto steroids to Δ^4-3-keto steroids (eq 1) have been reported[1,2] and they are limited to lyate species catalysis.[3] The present study is concerned primarily with the kinetics

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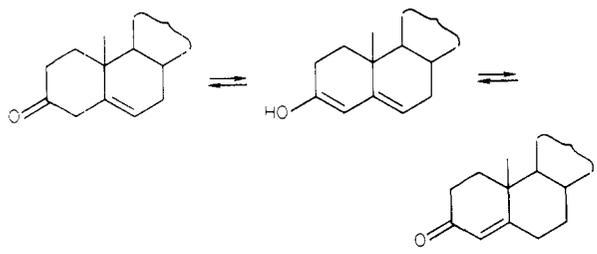

(1)

and mechanism of amine-catalyzed isomerization of androst-5-ene-3,17-dione (1) to androst-4-ene-3,17-dione (2) and of 17α-ethynyl-17β-hydroxy-5-estren-3-one (3) to 17α-ethynyl-17β-hydroxy-4-estren-3-one (4) and was undertaken with a view to presenting this chemistry as an alternative to that of acid-catalyzed isomerization[4] as a model for mechanisms of Δ^5-3-keto steroid isomerases.[4-11]

Experimental Section

Apparatus. A Gilford Model 2400 spectrophotometer and a Cary Model C118 spectrophotometer were used for collection of kinetics data and for UV scans. A Tamson T9 water bath was used to circulate water at constant temperature (±0.1 °C) through thermospacers in the Gilford spectrophotometer or through the cuvette holder in the Cary spectrophotometer. A Radiometer PHM 26 was used to measure pH, a Varian Model T60A spectrometer was used to obtain NMR spectra, and a Perkin-Elmer Model 727B was used for IR spectra.

Reagents. Reagents were Fisher certified ACS grade except the following: 2-(dimethylamino)ethanol, 3-(dimethylamino)-propylamine, 3-(dimethylamino)propanol, *N*-methylpiperidine, *N*-methylmorpholine, quinuclidine, quinuclidinol (Aldrich); aminoethanol, triethylamine, *N*,*N*-dimethyl-*tert*-butylamine (Eastman); 17α-ethynyl-17β-hydroxy-5(10)-estren-3-one (3), 17α-ethynyl-17β-hydroxy-4-estren-3-one (4) (Sigma); D_2O, DCl (99.8% D, Stohler Isotope Chemicals). Line-distilled water was redistilled through a Corning AG la still before use. **Androst-5-ene-3,17-dione (1)** was prepared by the method of Djerassi et al.[12] and was further purified by using thick-layer chromatography with silica gel PF 254 and methylene chloride–ethyl acetate (5:1 v/v) as solvent. The product was removed from the gel band with ethyl acetate, the silica gel was filtered through Celite, and the ethyl acetate was removed on a rotary evaporator. The resulting oil was dissolved in anhydrous ether, and the ether was evaporated on a rotary evaporator to give an oil which solidified to white crystalline 1: mp 137–139 °C with softening at 113 °C (lit. mp 119–125 °C with softening at 115 °C,[12,13] 156–158 °C,[14] 153–154 °C,[15,16] 167–169 °C,[17] 137–142 °C[18]); IR ($CHCl_3$) 1728 cm^{-1}, no carbinol absorption; UV essentially flat from 225 to 400 nm, ϵ_{248} (H_2O) 703 M^{-1} cm^{-1} (lit.[12] ϵ_{240} 302 M^{-1} cm^{-1}). **Androst-4-ene-3,17-dione (2)** was prepared by Oppenauer oxidation of dehydroisoandrosterone (Aldrich) and was purified on silica gel (60–200 mesh) by using $CHCl_3$ with increasing amounts (4, 8, 15, and 25% v/v) of ether: mp 169–170 °C (lit. 174 °C,[19] 169–170 °C,[17] 172–175 °C,[13]); UV (H_2O) λ_{max} 248 nm (log ε 4.2) (lit. log ε 4.2[6], 4.3[13]); IR ($CHCl_3$) 1665, 1737 cm^{-1}.[20]

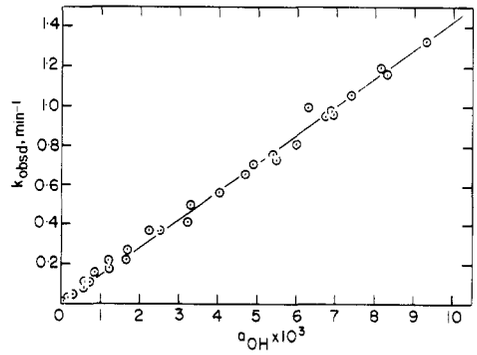

Figure 1. Plot of the pseudo-first-order rate constant, k_{obsd}, vs. the activity of hydroxide ion, a_{OH}, for isomerization of **1** to **2** (μ = 0.5 M (KCl)). For isomerization in dilute KOH solution (a_{OH} = 6.76 × 10^{-3}) with no added KCl, k_{obsd} = 0.950 min^{-1} (cf. graph).

Kinetics. Pseudo-first-order reactions [t = 30 ± 0.1 °C, μ = 0.5 M (KCl)] were initiated by addition of 10 μL of Δ^5-3-keto steroid in absolute ethanol to acidic/basic reactants contained in 3-mL cuvettes; the final concentration of steroid was ca. 5 × 10^{-5} M. For serial dilutions of aqueous reactants, the pH was constant to within 0.03 pH. pK_a's were determined by the method of fractional neutralization. The pD was obtained by adding 0.4 to the pH meter reading.[21] pK_w = 13.83[22] and pK_w (D_2O) = 14.65[23] were used. Hydroxide activity was computed from K_w/a_H where $a_H = 10^{-pH}$. Production of Δ^4-3-keto steroid was monitored at 248 nm, and pseudo-first-order rate constants for isomerization of **1** and **3** catalyzed by tertiary amines, for isomerization of **1** with tris(hydroxymethyl)aminomethane, and for isomerization of **3** with 3-(dimethylamino)propylamine were calculated from slopes of plots of ln $[(OD_\infty - OD_0)/(OD_\infty - OD_t)]$ vs. time; the plots were linear to 75% reaction or beyond.

Reaction of **1** and **3** with 1 M aminoethanol was characterized by a rapid increase in OD at 280 nm followed by a slower decrease in OD at 280 nm and a parallel slow increase in OD at 248 nm. At 280 nm an initial rapid increase followed by a slower decrease in OD gave pseudo-first-order kinetics when the OD vs. time data were treated for an A to B to C reaction sequence.[24,25] At amine concentrations less than ca. 0.2 M aminoethanol it was not possible to observe an A to B to C pattern; only a slow OD increase was observed, and pseudo-first-order plots were curved. Efforts to obtain satisfactory pseudo-first-order plots by using data collected at 248 nm at low aminoethanol concentrations were unsuccessful.[26] Reaction of **1** in 0.2 M Tris buffer (pH 8.15) showed only an OD increase with time at 248 nm.

Products. In general, comparison of UV spectra of product solutions, following reactions of **1** and **3** with dilute acids and bases, with those of authentic **2** and **4** showed that the major products were **2** and **4**, respectively. In dilute HCl solution, isomerization of **1** to **2** and **3** to **4** is quantitative via UV spectroscopy. In 0.1 M quinuclidine solution (pH 9.95) isomerization of **1** to **2** is quantitative via UV spectroscopy. A solution of 15.4 mg of **1** in

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(26) We were unable to obtain pseudo-first-order kinetics in solutions of less than 0.2 M aminoethanol by monitoring the reaction at several wavelengths. It appears as though hydrolysis of Schiff bases becomes faster than isomerization at low aminoethanol concentrations but not sufficiently so to give satisfactory kinetics.

Table I. Rate Data for Isomerization of 1 to 2 in Aqueous Solution[a]

catal[b]	k_2, M^{-1} min^{-1} [c]	f_B	concn range of catal, M	no. of k_{obsd} values
DMAE	2.65 ± 0.35	0.2, 0.4, 0.75	0.005-0.5	86
DMAE (D_2O)	0.437 ± 0.014	0.5	0.01-0.1	10
DMAP	8.62 ± 1.34	0.4, 0.5, 0.6	0.05-1.0	30
DMAP (D_2O)	0.93 ± 0.02	0.5	0.05-0.5	10
NMM	0.33 ± 0.006	0.5	0.1-1.0	10
NMP	8.96 ± 0.15	0.5	0.05-0.5	10
Qol	37.3 ± 0.21	0.5	0.025-0.25	10
Q	84.1 ± 2.04	0.5	0.02-0.2	10
TEA	2.19 ± 0.02	0.3, 0.6	0.05-0.7	20
OH^-	150 ± 15		$(0.1\text{-}9.3) \times 10^{-3}$ [d]	99
HCl	1.36 ± 0.03		0.1-0.5	6
CAA	0.062 ± 0.003	0.1, 0.2, 0.4, 0.6	0.05-0.45	15
MAA	0.016 ± 0.001	0.44	0.1-0.5	5
Tris	0.119 ± 0.002	0.5, 0.85	0.05-0.5	9

[a] t = 30 °C, μ = 0.5 M (KCl). [b] (Dimethylamino)ethanol (DMAE), pK_a = 9.35 (9.98 in D_2O); (dimethylamino)propanol (DMAP), pK_a = 9.56 (10.23 in D_2O); *N*-methylmorpholine (NMM), pK_a = 7.73; *N*-methylpiperidine (NMP), pK_a = 10.29; quinuclidinol (Qol), pK_a = 9.98; quinuclidine (Q), pK_a = 11.28; triethylamine (TEA), pK_a = 10.78; tris(hydroxymethyl)-aminomethane (Tris), pK_a = 8.15; chloroacetic acid (CAA), pK_a = 2.85; methoxyacetic acid (MAA), pK_a = 3.53. [c] For amines, $k_2 = k_A$ of eq 2; for OH^-, HCl, and carboxylic acids, $k_2 = k_{OH}$ (eq 2), k_H (eq 5), and k_{HA} (eq 6), respectively. [d] a_{OH}.

20 mL of 50% aqueous methanolic KOH (5×10^{-3} M) was kept at room temperature until reaction was complete. The solution was acidified to pH 6.5, and solvent was removed on the rotary evaporator (40 °C). The residue was stirred with CH_2Cl_2 (4 × 10 mL), and the combined CH_2Cl_2 solutions were evaporated to give 15 mg (97%) of solid: mp 168–170 °C; TLC on silica gel (Type K301R, Eastman) with 0.5% C_2H_5OH in CH_2Cl_2 showed one spot with R_f 0.36, identical with authentic **2** and different from **1** (R_f 0.63). Similarly, a solution of 15.4 mg of **3** in 40 mL of 50% aqueous methanolic KOH (0.01 M) was kept at room temperature until reaction was complete. The solution was acidified to pH 5, and solvent was removed on the rotary evaporator (40 °C). The residue was stirred with ether (4 × 10 mL), and the combined ether solutions were evaporated to give 13.3 mg (86%) of tan solid: mp 202 °C; TLC on silica gel (Type K301R, Eastman) with 5% ethyl acetate in $CHCl_3$ showed a strong spot with R_f 0.41, identical with authentic **4** and different from **3** (R_f 0.55). As well, there was a very faint spot with R_f 0.7 which was not identified. Acidification of reaction solutions from high-pH runs in dilute KOH or in tertiary amine buffers resulted in no additional time-dependent OD change, showing that no spectroscopically detectable amount of **2** or **4** is present following base-catalyzed isomerization.

Kinetics Results

In dilute aqueous tertiary amine solutions isomerizations of **1** and **3** give the rate law of eq 2, where f_B is the fraction

$$v/[\Delta^5] = k_{obsd} = k_A f_B[A_t] + k_{OH}a_{OH} \quad (2)$$

of free amine in the reactant buffer and $[A_t]$ is the molar concentration of total amine species (A + AH). The rate constants k_A (Tables I and II) were obtained by dividing the slopes of plots of k_{obsd} vs. $[A_t]$ by f_B. The values[27] of k_{OH} reported in Tables I and II were obtained as the slope

Table II. Rate Data for Isomerization of 3 to 4 in Aqueous Solution[a]

catal[b]	k_2, M^{-1} min^{-1}	f_B	concn range of catal, M	no. of k_{obsd} values
DMAE	0.0056 ± 0.0004	0.5	0.1-1.0	10
NMM[c]	0.00134 ± 0.00006	0.5	0.02-0.20	6
DMTBA	0.096 ± 0.012	0.5	0.01-0.1	10
Qol	0.18 ± 0.0058	0.5	0.05-0.5	10
Q	1.42 ± 0.003	0.5	0.02-0.2	10
Q (D_2O)	0.248 ± 0.001	0.5	0.02-0.2	10
DMAPA	3.41 ± 0.16	0.5, 0.75	0.01-0.1	20
OH^-	18.7 ± 1.8		0.01-0.07	14
HCl[d]	0.051 ± 0.007		0.10-1.0	12

[a] t = 30 °C, μ = 0.5 M (KCl). [b] (Dimethylamino)ethanol (DMAE), pK_a = 9.35; *N,N*-dimethyl-*tert*-butylamine (DMTBA), pK_a = 10.53; quinuclidinol (Qol), pK_a = 9.98; quinuclidine (Q), pK_a = 11.28 (11.93 in D_2O); (dimethylamino)propylamine (DMAPA), pK_a 10.38. [c] Data obtained from initial velocities. [d] μ = 1.0 M (KCl).

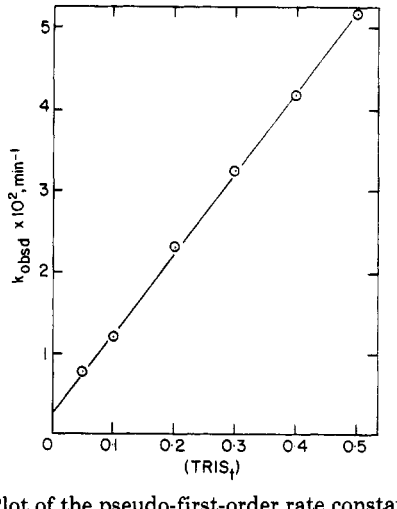


Figure 2. Plot of the pseudo-first-order rate constant, k_{obsd}, vs. the molar concentration of Tris (pH 8.91, f_B = 0.85).

(27) There is a discrepancy between the value of k_{OH} = 150 ± 15 M^{-1} min^{-1} (Table I, Figure 1) obtained in this study and the literature[2] value of 973 M^{-1} min^{-1} for isomerization of **1**. A referee requested we account for this discrepancy, and we offer the following observations. First, the literature value was obtained from k_{obsd} for isomerization of **1** in 0.05 M Tris buffer, and it was assumed that Tris did not catalyze isomerization. Figure 2 shows that this assumption is not valid, and it can be seen that k_{obsd} in 0.05 M Tris (pH 8.92) is ca. 3 times the value of k_{obsd} obtained by extrapolation to zero buffer concentration. Second, the heat of ionization of water was not taken into account in the determination of a_{OH} ($\equiv k_w/a_H$); for six k_{OH}'s determined at six different temperatures, pK_w = 14 was apparently used throughout (Table II, ref 2). If pK_w (30 °C) = 13.83 is used, k_{OH} = 658 M^{-1} min^{-1}, and the factor of 3 introduced by Tris catalysis reduces the value of k_{OH} to ca. 200 M^{-1} min^{-1} (μ = ?). Finally, the reliability of k_{obsd} values appears to be questionable; use of the correct pK_w at each reported[2] temperature gives six k_{OH} values that decrease as temperature increases.

Table III. Rate Data for Isomerization of 1 and 3 Catalyzed by Aminoethanol and for Hydrolysis of the Imines of 2 and 4[a]

	k_{AE}^{i}	$10^3 k_{OH}^{i}$	k_{AE}^{h}	$10^3 k_{OH}^{h}$	f_B	concn range of AE	pH	no. of k_{obsd} values
1	3.64 ± 0.46	5.32 ± 1.6	0.89 ± 0.1	4.87 ± 0.34	0.5	0.1-0.5	9.5	10
3	1.57 ± 0.17	3.05 ± 0.5	0.66 ± 0.03	1.09 ± 0.27	0.24	0.2-0.63	8.9	8
3	1.08 ± 0.10	6.20 ± 0.4	0.64 ± 0.03	1.25 ± 0.19	0.33	0.24-0.75	9.25	8
3	0.69 ± 0.05	7.03 ± 0.4	0.49 ± 0.02	1.70 ± 0.15	0.5	0.3-1.0	9.50	8
3	0.69 ± 0.06	2.41 ± 0.2	0.69 ± 0.06	1.56 ± 0.25	0.76	0.4-1.0	10.0	7

[a] t = 30 °C; μ = 0.5 M (KCl); rate constants have units of M^{-1} min^{-1}.

of plots of k_{obsd} vs. a_{OH} (Figure 1) for reactions run in dilute KOH solution or in dilute pH 9.5–10.6 buffer solution; in the latter cases, k_{obsd} values for hydroxide ion catalysis were the intercepts of plots of k_{obsd} vs. buffer concentration (eq 2).

Tris(hydroxymethyl)aminomethane- (Tris) and (dimethylamino)propylamine-catalyzed isomerization of 1 to 2 and the kinetics follow eq 2 (Figure 2).

The deuterium solvent kinetic isotope effect $k_A(H_2O)/k_A(D_2O)$ for quinuclidine-catalyzed isomerization of 3 to 4 is 5.7; for (dimethylamino)propanol- and (dimethylamino)ethanol-catalyzed isomerization of 1 to 2, the isotope effects are 5.7 and 6, respectively.

The Brønsted relationship for isomerization of 1 to 2 catalyzed by quinuclidine, *N*-methylpiperidine, quinuclidinol, (dimethylamino)propanol, (dimethylamino)ethanol, and *N*-methylmorpholine has $\beta = 0.68 \pm 0.12$ ($r = 0.939$). That for isomerization of 3 to 4 catalyzed by quinuclidine, quinuclidinol, *N,N*-dimethyl-*tert*-butylamine, (dimethylamino)ethanol, and *N*-methylmorpholine hab $\beta = 0.84 \pm 0.18$ ($r = 0.941$).

Isomerization of 1 to the imine of 2 and of 3 to the imine of 4 catalyzed by aminoethanol (0.2–1.0 M) gives the rate law of eq 3; at the pHs employed, $k_{OH}a_{OH}$ is generally

$$v/[\Delta^5] = (k_{obsd} - k_{OH}a_{OH}) = k_{obsd}^{i} = k_{AE}^{i}f_B[AE_t] + k_{OH}^{i}a_{OH} \quad (3)$$

negligible. The values of k_{AE}^{i} (Table III) were obtained by dividing slopes of plots of k_{obsd} vs. $[AE_t]$ by f_B; the values of k_{OH}^{i} (Table III) were obtained by dividing intercepts of plots of k_{obsd} vs. $[AE_t]$ by a_{OH}. Hydrolysis of the 3-hydroxyethylimine of 2 and 4 gives the rate law of eq 4,

$$v/[\Delta^4\text{-imine}] = k_{obsd} = k_{AE}^{h}f_Bf_A^{im}[AE_t] + k_{OH}^{h}f_A^{im}a_{OH} \quad (4)$$

where f_A^{im} is the mole fraction of iminium ion, based on an assumed pK_a of 11 which is 1.5 logarithm units greater than that of aminoethanol.[41] The values of k_{AE}^{h} (Table III) were obtained by dividing the slopes of plots of k_{obsd} vs. $[AE_t]$ by $f_Bf_A^{im}$; the values of k_{OH}^{h} (Table III) were obtained by dividing the intercepts of plots of k_{obsd} vs. $[AE_t]$ by a_{OH}. No rate constant for water-catalyzed hydrolysis of the 3-hydroxyethylimine of 4 was detected.

In dilute acid solution, isomerizations of 1 to 2 and of 3 to 4 obey the rate law of eq 5. The values of k_H (Tables I and II) were obtained as slopes of plots of k_{obsd} vs. a_H. In the pD range 0.46–1 isomerization of 1 and 3 did not follow pseudo-first-order kinetics. Plots of ln $[(OD_\infty - OD_0)/OD_\infty - OD_t)]$ vs. time were nonlinear (Figure 3). Isomerization of 1 to 2 was catalyzed by chloroacetic acid and methoxyacetic acid according to the rate law of eq 6.

$$v/[\Delta^5] = k_{obsd} = k_Ha_H + k_{HA}f_{HA}[HA_t] \quad (5)$$

$$v/[\Delta^5] = k_{obsd} = k_Ha_H + k_{HA}f_{HA}[HA_t] \quad (6)$$

The values of k_{HA} (Table II) were obtained by dividing the slopes of plots of k_{obsd} vs. $[HA_t]$ by f_{HA}, the mole fraction of acid present in the catalytic buffer.

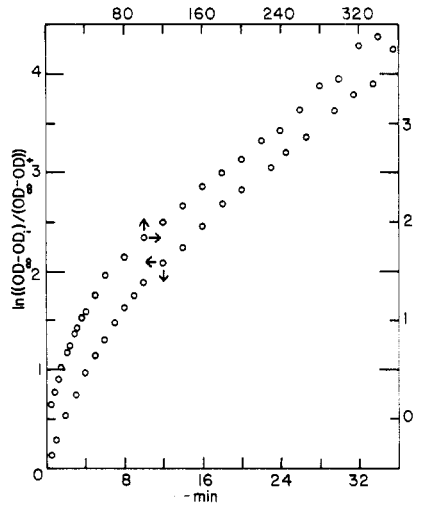
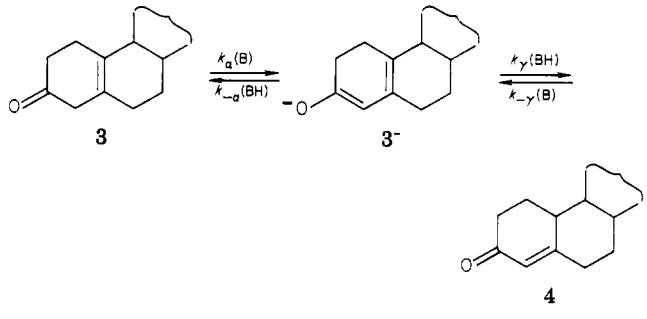


Figure 3. Plots of ln $[(OD_\infty - OD_i)/(OD_\infty - OD_t)]$ vs. time for isomerization of 1 to 2 (lower plot) in D_2O (pD 1.03) and for isomerization of 3 to 4 (upper plot) in D_2O (pD 0.44).

Scheme I



Base-Catalyzed Isomerization. A priori[1,2,28-37] base-catalyzed isomerization of Δ^5-3-keto steroids such as 3

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(38) Exchange of deuterium for hydrogen in 4,4-dideuterated 1 in Tris buffer (pH 8.8) or in hydroxide solution (pH 10) was reported[2] to occur at a significant rate as indicated by the reported curvilinear nature of the pseudo-first-order plot for isomerization. This suggests that partitioning of the 1 dienolate is important; i.e., the inequality $k_{-\alpha} > k_\gamma$ (Scheme I, eq 8) may not hold for 1 so that neither k_α nor k_γ is strictly rate determining. However, in the present study, pseudo-first-order plots for isomerization of 1 catalyzed by (dimethylamino)ethanol in D_2O were linear.

follows Scheme I. When a number of potassium dienolates were quenched in aqueous acetic acid, Δ^5 isomers were preferentially formed, showing that $k_{-\alpha} > k_\gamma$. If the steady-state condition is assumed for 3^-, the rate law for isomerization according to Scheme I is given by eq 7, where

$$\nu/(\Delta^5) = k_{obsd} = (k_f + k_r) = [(k_\alpha k_\gamma)/(k_{-\alpha} + k_\gamma)](1 + 1/K_e)[B] \quad (7)$$

$K_e = k_\alpha k_\gamma / k_{-\alpha} k_{-\gamma} = \Delta^4/\Delta^5$ and k_f and k_r are the pseudo-first-order rate constants for the forward and reverse reactions. For the conditions $k_{-\alpha} > k_\gamma$ and $K_e \gg 1$ (K_e was immeasurably large under the conditions of this study), eq 7 reduces to eq 8, where K_{SH} is the ionization constant

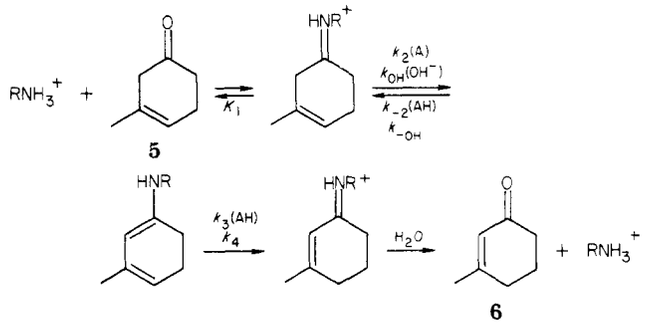
$$k_{obsd} = k_\gamma(K_{SH}/K_a)[B] \quad (8)$$

for 1 or 3 and K_a is the ionization constant for the general acid BH (Scheme I). Both eq 7 and eq 8 have the form of eq 2 for tertiary amine catalysis, so that the mechanism of Scheme I is in accord with the experimental results.

The mechanism of Scheme I, eq 8, for isomerization of 1 and 3 is supported by deuterium solvent kinetic isotope effects of ca. 6 for reactions of 1 and 3 with tertiary amines. In a related study an isotope effect of 7.7 was obtained for isomerization of 3-cyclohexenone to 2-cyclohexenone catalyzed by phosphate, and k(exchange)/k(isomerization) = 575.[30] Qualitatively similar results were obtained for isomerization of dimethyl methylenesuccinate to dimethyl mesaconate in methanol catalyzed by triethylamine.[34] Additional support for the mechanism is provided by the result that isomerization of 1, but not of 3, is catalyzed by triethylamine, suggesting that general acid catalyzed protonation of the 3 dienolate ion at C-10 is disfavored when sterically bulky triethylammonium ions are catalysts; here ammonium ion catalysis becomes noncompetitive with lyate species catalysis, and only the latter is detected. Protonation of the 1 dienolate ion at C-6 appears from models to be less subject to steric hindrance.

Androst-5-ene-3,17-dione (1) is more reactive than 3 which means that the value of $K_{SH}k_\gamma$ (eq 8) is larger for 1 than for 3. The following considerations indicate that the greater acidity of 1 than 3 controls the relative reactivity of these steroids. It is likely that 1 is a stronger acid than 3; i.e., the 1 dienolate ion is more stable than the 3 dienolate ion. This is based on the assumption that the C-4, C-5 dihedral angle for the 1 dienolate ion is ca. 0° and is less than that for the 3 dienolate ion, as suggested by molecular models, with resultant better orbital overlap in the 1 dienolate ion. Lane and Allinger[39] calculated diene dihedral angles of ca. 8–12° for several cis steroid dienes analogous to the 3 dienolate ion: we found no information on those angles for trans steroid dienes. However, experimental support for the relative values of the angles is found in the greater ϵ for cholesta-3,5(6)-diene (23 000 M^{-1} cm^{-1}) than for cholesta-2,4-diene (6500 M^{-1} cm^{-1}).[40] Considering relative k_γ values, we expect them to depend mainly on relative basicities of the 1 C-6 and 3 C-10 carbanions and on steric effects during protonation. The involvement of steric effects was shown by the result that triethylammonium ion catalyzed isomerization of 1 but not of 3. Steric effects aside, structure considerations suggest that the C-10 carbanion is more basic than the C-6 carbanion and k_γ should be greater for 3 than for 1. There is some experimental evidence to support this: α (k_γ) values ($\alpha = \beta^{exptl} - 1$) are ca. 0.15 for 3 and 0.3 for 1. The uncertainties in α values probably reflect the varying steric requirements of the different tertiary amines in the transition state; however, because 1 is more reactive than 3, we conclude that K_{SH} values determine the relative reactivity here.

Scheme II



Reactions of 1 and 3 with Ethanolamine. Isomerization of 1 to 2 was shown to be catalyzed by primary amines, and a number of lines of evidence support the existence of a rapidly formed Δ^4-3-imine which hydrolyzes slowly to 2; no rate data were reported.[18] In a related study,[41] the kinetics of isomerization of 3-methyl-3-cyclohexenone (5) to 3-methyl-2-cyclohexenone (6) and of 1-acetyl-2-cyclohexene (7) to 1-acetyl-1-cyclohexene (8) catalyzed by trifluoroethylamine were examined, and for 5 isomerization was shown to proceed via formation of trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylamine, the Schiff base of 5: no Schiff base was detected for reactions of 7 with trifluoroethylamine. The proposed mechanism is shown in Scheme II.

Isomerization of 1 to 2 and of 3 to 4 was catalyzed by ethanolamine at rates faster than those for isomerization catalyzed by (dimethylamino)ethanol of comparable pK_a. The observed UV spectral characteristics of these reactions were similar to those described by Benisek and Jacobsen[18] for isomerization of 1 catalyzed by glycylglycine and by Pollack and Kayser[41,42] for isomerization of 5 to 6. Isomerization of 1 and 3 catalyzed by ethanolamine is characterized by a rapid OD increase at 280 nm, which we ascribe to formation of a conjugated Schiff base, and a slower decrease in OD at 280 nm, accompanied by an OD increase at 248 nm, which we ascribe to hydrolysis of the Schiff base to give 2 and 4. The rate law for isomerization of 1 and 3 in the concentration range 0.2–1 M aminoethanol is given by eq 3 and is different from that for isomerization of 5 to 6.[41] For isomerization of 1 and 3, the rate law of eq 9

$$\nu/[S_t] = k_{obsd} = \{(k_2k_3[A][AH] + k_3k_{OH}[AH][OH^-] + k_2k_4[A] + k_{OH}k_4[OH^-])K_1[AH]\}/\{((k_{-2} + k_3)[AH] + k_{-OH} + k_4)(K_1[AH] + 1)\} \quad (9)$$

can be obtained from Scheme II. If for isomerization of 1 and 3 we assume that $K_1[AH] > 1$, that $(k_{-2} + k_3)[AH] > (k_{OH} + k_4)$, and that $k_{OH}k_4[OH]/(k_{-2} + k_3)[AH]$ goes to zero, eq 9 reduces to eq 10 which has the form of eq 3. We

$$\nu/[S_t] = k_{obsd} = (k_2k_3[A] + (k_3k_{OH} + k_2k_4K_a/K_w)[OH^-])/(k_{-2} + k_3) \quad (10)$$

believe that the spectral and kinetics results are adequate to allow the conclusion that the mechanism of Scheme II

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is a fair representation of the chemistry that occurs.

Hydrolysis of the 2 and 4 Iminium Ions. Hydrolysis of iminium ions formed during isomerization of 1 and 3 kinetically followed established patterns.[43] Thus general-base catalysis of hydrolysis of an iminium ion by aminoethanol and nucleophilic attack by hydroxide ion on the iminium ion are routes to 2 and 4. We did not attempt to determine the pK_a of the iminium ions but assumed the pK_a to be greater than that of aminoethanol. Pollack and Kayser[41] determined the value of the pK_a of 2,2,2-trifluoro-*N*-(3-methyl-2-cyclohexenylidene)ethylammonium ion and found it to be a unit greater than the pK_a of trifluoroethylamine. In the present study we found that statistically, the best set of rate constants, k_{EA}^h and k_{OH}^h using eq 5, were generated by assuming the fraction of iminium ion was 1 throughout the pH range 8.9–10; effectively this assumption requires the pK_a to be ca. 11.

Acid-Catalyzed Isomerization. There are two kinetics reports of the acid-catalyzed isomerization of Δ^5- to Δ^4-3-keto steroids. In one of them, a study of the comparative reactivity of six $\Delta^{5,6}$-3-keto steroids, Nes et al.[13] found that the $\Delta^{5,6}$-3-keto steroids are about 10-50 times more reactive than the $\Delta^{5,10}$-3-keto steroids. In the other, a mechanisms study of the isomerization of 1 to 2, Malhotra and Ringold[4] concluded that enolization is rate determining on the basis of primary and deuterium solvent kinetic isotope effects and product isolation studies. In the present study, the values of the rate constants for isomerization of 1 and 3 (Tables I and II) are in very good agreement with those published.[4,13] The result that chloroacetic acid and methoxyacetic acid catalyze the isomerization of 1 supports rate-determining enolization as postulated;[4] this process is well-known to be general acid–base catalyzed. However, the curvilinear plots shown in Figure 3 for isomerization of 1 and 3 in D_2O/DCl suggest that 1 and 3 exchange C-4 protons with solvent during isomerization, and enolization is not cleanly rate determining. We are unaware of other enolization reactions that suggest that partitioning of an enol is kinetically important.[47] The approximate limiting rate constants obtained for short and long times give $k_2(H_2O)/k_2(D_2O)$ values of about 0.5 and 2, respectively. The former KIE is similar to those reported for the enolization of acetone,[44-46] and the latter is reasonable for rate-determining protonation of O-deuterated dienol. Further, the conclusion that partitioning of dienols is kinetically important during isomerization is supported by results of product-isolation studies carried out by Malhotra and Ringold, who found that isomerization of 17β-hydroxyandrost-5-en-3-one to 17β-hydroxyandrost-4-en-3-one, when taken to 50% completion, gave starting material containing 0.08 atom of deuterium at C-4.[4] Clearly, partitioning of dienol to product is kinetically favored over partitioning to starting material in this case.

The following conclusions of mechanism can be drawn from results of this study. (1) In solutions of tertiary amines, C-6 protonation of the 1 dienolate and C-10 protonation of the 3 dienolate are rate determining. (2) From a consideration of Brønsted β's, it may be concluded that the greater reactivity of 1 than 3 is due to the greater concentrations of the 1 dienolate than those of the 3 dienolate ions. (3) In solutions of aminoethanol, 1 and 3 rapidly form Schiff bases whose reactivity in isomerization markedly exceeds the reactivities of 1 and 3 with tertiary amines such as (dimethylamino)ethanol, but slow hydrolysis of the Schiff bases undercuts the efficiency of such catalysis. (4) In DCl/D_2O solutions partitioning of dienols is kinetically detectable. (5) Base-catalyzed isomerization is more efficient than acid-catalyzed isomerization.

Registry No. 1, 571-36-8; 2, 63-05-8; 3, 68-23-5; 4, 68-22-4.

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(47) Depending on substitution patterns, acid-catalyzed isomerization of 3-cyclohexen-1-ones occurs via rate-determining enolization or rate-determining protonation of dienols. Here the existence of dienol in acid-catalyzed isomerization of unconjugated ketones is clearly demonstrated.[48,49]
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Double-Bond-Stabilizing Abilities of Dimethylamino, Alkylsulfonyl, and Acetyl Substituents[1]

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Equilibrium constants have been determined for the isomerization of *trans*-$XCH_2CH{=}CHY$ to *trans*-$XCH{=}CHCH_2Y$ for three combinations of X and Y. The values obtained were 40 ± 15 for X = dimethylamino and Y = phenyl, 40 ± 15 for X = methyl and Y = *n*-butylsulfonyl, and 4.8 ± 0.5 for X = acetyl and Y = methyl. These data give *D* values (double-bond-stabilizing parameters) of 8.2, −0.1, and 3.36 kcal/mol for dimethylamino, *n*-butylsulfonyl, and acetyl substituents, respectively. The dimethylamino substituent is thus by far the best double-bond-stabilizing substituent that has been studied. The equilibrium constant for isomerization of *n*-butyl *trans*-1-butenyl sulfone is about eight times as large as that reported by other workers and it yields a *D* value for the *n*-butylsulfonyl group that is much nearer the value for the methylsulfonyl group. The *D* value for acetyl is near that found earlier for carbomethoxy.

It has been previously shown that a consistent scale of double-bond-stabilizing abilities may be obtained from data on equilibria such as eq 1, if allowance is made for the interaction of X and Y across the carbon–carbon

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