Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.20; H, 10.64.

4,4-Dimethylandrostane-3β,17β-diol (Va). (*a*) *By borohydride reduction of* IIIa. Sodium borohydride reduction of saturated ketone IIIa by the usual procedure furnished in 88% yield, 4,4-dimethylandrostane-3β,17β-diol (Va), m.p. 245–247°, $[\alpha]_D$ −16°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.68; H, 11.01.

(*b*) *By catalytic hydrogenation of* IVa. The hydrogenation at 25° and atmospheric pressure of 300 mg. of IVa in 15 cc. of methanol over 150 mg. of 10% prereduced palladium-carbon was complete after 2 hr., with 33 cc. hydrogen uptake (theoret. 30 cc.). Crystallization of the crude product from acetone gave 210 mg. of Va, m.p. 245–247°, identical in all respects with the product obtained by hydride reduction of IIIa.

4,4,17-Trimethylandrostane-3β,17β-diol (Vb). The trimethyldiol (Vb) was derived in 87% yield by sodium borohydride reduction of IIIb in aqueous tetrahydrofuran solution. The analytical sample from acetone melted at 230–234°, $[\alpha]_D$ −28°.

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 79.14; H, 11.56.

Keto Acid (VI). The keto acid VI, m.p. 200–202°, was prepared in 76% yield by ozonization of testosterone as described by Weisenborn, Remy, and Jacobs.[11b]

Enol Lactone (VII). A mixture of 5 g. of VI and 5 g. of sodium acetate was heated in 125 cc. of boiling acetic anhydride for 21 hr. The solvent was removed *in vacuo*, ice water was added, the mixture extracted with ethyl acetate, the organic phase washed with cold 1% potassium carbonate solution and evaporated to dryness. Crystallization of the residue from hexane gave 4.6 g. (85%) of enol lactone (VII), m.p. 125–130°, which was used without further purification. Fujimoto[12] reports m.p. 129–133° for an analytical specimen of VII.

4-Methyltestosterone (IX). A stirred solution of 3 g. of enol lactone (VII) in 40 cc. of anhydrous ether and 10 cc. of anhydrous tetrahydrofuran was treated dropwise, at 0°, with 4 cc. of a 3*N* ethereal solution of ethyl magnesium bromide. The mixture, under nitrogen, was stirred for 1.5 hr. at ice bath temperature, at 25° for an additional 16 hr. and finally poured into ice water and acidified with dilute hydrochloric acid. The ether extract, after successive washing with 4*N* hydrochloric acid, water, 2% sodium bicarbonate and water, was taken to dryness, the residue dissolved in 260 cc. of methanol and a solution of 9 g. of sodium hydroxide in 45 cc. of water was added. The solution, after 3 hr. of boiling under nitrogen, was neutralized with acetic acid, concentrated to a volume of *ca.* 50 cc., poured into water, the steroid extracted with ethyl acetate, and the ethyl acetate extract washed with water and evaporated to dryness.

The product, dissolved in 200 cc. of benzene, was subjected to chromatographic purification on a column of 150 g. of alkaline alumina. Pooling of the crystalline benzene-ether fractions (8:2) and recrystallization from acetone-hexane gave 730 mg. (27%) of 4-methyltestosterone (IX), m.p. 169–171°, $[\alpha]_D$ +121° (chloroform), λ_{max} 250 mμ, log ε 4.21, infrared carbonyl absorption band at 1660 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.45; H, 10.10.

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[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA, UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

Reactivity Studies on Natural Products. II.[1] Kinetics of Bromination of Some Steroid Ketones

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The rates of bromination of cholestan-3-one, coprostan-3-one, 6- and 7-ketocholestane, and, for comparison, cyclopentanone and cyclohexanone, have been measured in 90% acetic acid containing 0.06*M* hydrogen chloride The results show that both the rate-determining enolization and the approach of the bromine are important steps.

The reactivity of some steroid ketones toward hemiketal formation has been recently reported,[1] but no kinetic study has been made of reactions involving the enolic form of the ketone. The acid-catalyzed bromination of ketones involves enol formation as the rate-determining step,[2] and accordingly the rates of bromination of cholestan-3-one, coprostan-3-one, 6- and 7-ketocholestane, cyclopentanone and cyclohexanone, have been measured (see Table I), to investigate the influence of differences in ring fusion and ring position on ketone enolization.

TABLE I
BROMINATION OF KETONES

	75% Acetic Acid[a] k × 10^5[b]	90% Acetic Acid[c] k × 10^5[b]	Ratio[d]
Cyclopentanone	1.91 ± 0.05	4.61 ± 0.04	0.34
Cyclohexanone	6.25 ± 0.11	13.4 ± 0.5	1.0
Cholestan-3-one		29.5 ± 0.6	2.2
Coprostan-3-one		22.6 ± 0.5	1.7
6-Ketocholestane		1.62 ± 0.02	0.12
7-Ketocholestane		0.910 ± 0.015	0.068

[a] Containing 0.10*M* hydrogen chloride. [b] At 25.0 ± 0.1°. [c] Containing 0.0617*M* hydrogen chloride. [d] Radio of rates in 90% acetic acid to cyclohexanone = 1.0.

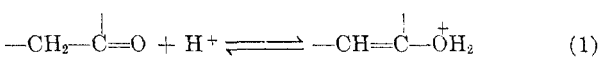
It is known that 3-keto-steroids of the allo-series (rings A/B trans), *e.g.* cholestan-3-one, undergo bromination in position 2, whereas the corresponding ketones of the normal series (rings A/B cis), *e.g.*, coprostan-3-one, give the 4-bromo ke-

(1) Part I. *Anal. Chem.*, **29**, 538 (1957).

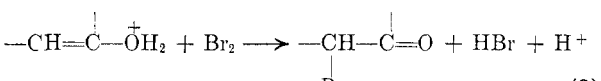
(2) (a) A. Lapworth, *J. Chem. Soc.*, **85**, 30 (1904); (b) H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, 2430 (1951).

tone.[3] Also 6-ketosteroids form 5-bromo derivatives,[4] but 7-ketosteroids give the 6-bromocompound.[5] From the present kinetic study the order of the rates of bromination was found to be cholestan-3-one > coprostan-3-one > cyclohexanone > cyclopentanone > 6-ketocholestane > 7-ketocholestane. Any detailed mechanism of bromination of cyclic ketones must explain both the differences in position of attack and the differences in rate.

The acid-catalyzed bromination of ketones has been shown to be first order in ketone, but independent of the bromine concentration,[2a] and these results have been interpreted as indicating a slow rate-determining reversible enolization of the ketone (1), followed by rapid attack of bromine (2).[6] In the



(1)



(2)

enolization of a cyclic ketone an axial hydrogen atom will be lost,[7a] since this allows of greater conjugation in the transition state. Similarly, addition of bromine to the once-formed enol will take place by axial attack which is the least hindered direction of attack upon a cyclohexene ring. An α-axial-bromo compound is always the initial product of the reaction.[7,8]

The greater reactivity of cyclohexanone as compared to cyclopentanone is consistent with the smaller extent of enol formation of the latter,[9] and with the generalization[10] that reactions proceed in such a manner as to favor retention of a double bond exocyclic to a five-membered ring and to avoid retention of a double bond exocyclic to a six-membered ring. In the case of cholestan-3-one, bromination takes place in position 2,[3,11] since there is greater hyperconjugative stabilization of the 2,3 double bond with respect to the 3,4 double bond,[12a] and smaller crowding between the C-10 angular methyl group and the axial hydrogen atoms at C-6[12c] with the former double bond. Moreover, formation of the 2,3 enol bends the hydrogen atom at C-2 away from the angular methyl group at C-10, and enolization will reduce the non-bonded interactions present in the present ketone, and the rate of bromination will be greater than that of cyclohexanone. Similarly, enol formation in the 3,4 position of coprostan-3-one[11] reduces the non-bonded interactions of the equatorial hydrogen atom at C-4 with the axial hydrogen atoms on carbons 7 and 9,[12a] whereas introduction of a Δ^2-double bond only reduces interactions on C-3 and C-9. This reduction of the non-bonded interactions also gives an enhanced rate of bromination.

A steroid 6-keto group can enolize by losing either the tertiary axial hydrogen atom at C-5 or a secondary hydrogen atom from C-7, but the rate of loss of a tertiary hydrogen atom will be much greater, and bromination will take place in position -5. However, introduction of this double bond will produce strain in both rings A and B, since all bond angles are slightly distorted[12c] and also the attack of a solvent molecule to remove the proton during enolization[2b] will be hindered by the axial hydrogen atoms at C-3 and C-7. For these reasons the observed rate of bromination is much less than that of cyclohexanone. In contrast to cholestan-3-one and coprostan-3-one, where enolization reduces the strain in the parent ketone, in the case of 6-ketocholestane enolization considerably increases the strain in the system.

For the 7-ketone enolization can again take place in two directions, involving either the tertiary axial hydrogen atom at C-8, or a secondary hydrogen atom at C-6. Loss of a tertiary hydrogen atom is generally more favored, but in this case approach from the top side of a solvent molecule to the axial hydrogen atom at C-8, and subsequent attack of the large bromine atom on the once-formed enol is impeded by the angular methyl groups on C-10 and C-13, and hence reaction will involve the 6,7 enol.[13] Thus for steric reasons bromination will take place

(3) A. Butenandt and L. Mamoli, *Ber.*, **68**, 1854 (1935); A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935); A. Butenandt, G. Schramm, A. Wolff, and H. Kudszus, *Ber.*, **69**, 2779 (1936); L. Ruzicka, W. Bosshard, W. H. Fischer, and H. Wirz, *Helv. Chim. Acta*, **19**, 1147 (1936).

(4) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 801 (1937); I. M. Heilbron, J. Jackson, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 102 (1938); R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 352 (1955).

(5) T. Barr, I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.* 334 (1938); D. R. James and C. W. Shoppee, *J. Chem. Soc.*, 1064 (1956).

(6) *Cf.* C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 536. J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, N. Y., 1956, p. 198.

(7) (a) E. J. Corey, *J. Am. Chem. Soc.*, **76**, 175 (1954); (b) D. A. H. Taylor, *Chemistry & Industry*, 250 (1955).

(8) The ketonization of enols has also been shown to proceed by addition of a proton from the least hindered side. H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955); *J. Amer. Chem. Soc.*, **78**, 1168 (1956).

(9) G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 656, 669, (1947).

(10) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(11) Cholestan-3-one also forms Δ^2 enol acetates and ethers, whereas coprostan-3-one forms the Δ^3 derivatives. W. G. Dauben, R. A. Micheli, and S. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952); M. Ruben and B. H. Armbrecht, *J. Am. Chem. Soc.*, **75**, 3513 (1953); H. H. Inhoffen, W. Becker and G. Kolling, *Ann.*, **568**, 181 (1950); H. H. Inhoffen, G. Kolling, G. Koch, and I. Nebel, *Ber.*, **84**, 361 (1951).

(12) (a) D. A. H. Taylor, *Chemistry & Industry*, 250 (1954); (b) A. S. Dreiding, *Chemistry & Industry*, 1419 (1954); (c) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955).

(13) The Δ^6-enol acetate is also formed. R. Hirschmann and N. C. Wendler, *J. Am. Chem. Soc.*, **75**, 2361 (1953).

in position 6,[14] and at a reduced rate since an equilibrium will exist between the two enols, which will favor the Δ^7 isomer. The small difference between the tertiary bromination of the 6-ketone and secondary bromination of the 7-ketone must be due to the fact that the Δ^6 double bond, in contrast to a Δ^5 double bond, introduces little strain in ring A. The 7- position is unique in its steric environment. An 11-ketone gives normally a 9-bromo derivative[15a] and $\Delta^{9(11)}$-enol acetate,[14, 15b] since approach to the underside of the molecule is not hindered.

EXPERIMENTAL

Ketones. These were highly purified specimens which had been prepared in a previous study.[1]

Solvents. Acetic acid (Baker Analyzed) was refluxed with and fractionated from chromium trioxide and acetic anhydride, and the fraction boiling at 107–108°/580 mm. was used. Acetic acid (1.8 l.) was diluted with distilled water to 2 l. and the solvent had d_4^{25} 1.0487. Hydrogen chloride, generated from analytical grades of hydrochloric and sulfuric acids, was passed into a portion of this acetic acid solution to give a 0.6171*M* solution. The hydrogen chloride was determined by adding aliquots to dilute nitric acid containing excess silver nitrate and titrating the excess silver nitrate with potassium thiocyanate. Bromine (Baker Analyzed) was added to the hydrochloric-acetic acid solution to about 0.05*M*. Its concentration was determined before each experiment, as described below.

A weighed quantity of ketone (0.2–0.3 g.) was dissolved in 90% acetic acid (*ca.* 80 ml.) in a 100 ml. graduated flask and allowed to equilibrate in temperature in a constant temperature bath maintained at 25.0 ± 0.1°. Ten milliliters of the stock solution of bromine were added and the volume quickly made up to the mark. Aliquots were withdrawn at various times and added to excess potassium iodide in water (*ca.* 20 ml.). The liberated iodine was titrated with sodium thiosulfate (0.05*M*), using starch as indicator.[16] Each experiment was repeated 3 or 4 times, and the rate constants for the first order reaction were obtained graphically. Linear plots were obtained up to about 60% reaction, but showed divergencies after this due to the catalytic action of the hydrogen bromide formed in the reaction, and to polybromination.[17]

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(14) A similar steric effect has been suggested to explain the course of enol acetate formation. A. Crawshaw, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 731 (1954).

(15) (a) H. B. Henbest, E. R. H. Jones, A. A. Wagland, and T. I. Wrigley, *J. Chem. Soc.*, 2477 (1955); (b) D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones and T. Walker, *J. Chem. Soc.*, 747 (1954).

(16) *Cf.* D. P. Evans, *J. Chem. Soc.*, 785 (1936).

(17) Cholestan-3-one has been shown to absorb about 3 moles of bromine during one day, followed by uptake of a fourth in 5 days. D. H. R. Barton, J. F. McGhie, M. K. Pradhan, and S. A. Knight, *J. Chem. Soc.*, 876 (1955).

[CONTRIBUTION FROM THE LABORATORIES OF G. D. SEARLE AND COMPANY]

4,5-Epoxy-3-oxo Steroids

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Several 3-keto-Δ^4 steroids have been converted to the corresponding epoxides. Both the α and the β epoxides of progesterone were isolated.[2] Fermentation of 4,5-epoxypregnane-3,20-dione (I) by *Rhizopus nigricans* led to the isolation of 4β,5-epoxy-11α-hydroxypregnane-3,20-dione. Treatment of I with formic acid gave 4-hydroxyprogesterone (IV).[3]

As the preliminary step to investigating a hypothesis[4] that biological 11β-hydroxylation proceeds through the 4,5-epoxy-3-oxo steroid, a number of the 4,5-epoxides were prepared and a few of their reactions studied.[5]

The epoxides were prepared by alkaline hydrogen peroxide oxidation of the corresponding conjugated ketones. Table I summarizes the analytical data and physical constants of these oxides. Plattner, Heusser, and Kulkarni[6] have shown that 4-

(1) Present address: American Chemical Society Applied Journals, Chicago.

(2) W. Cole and P. L. Julian [*J. Org. Chem.*, 19, 131 (1954)] described an epoxide of progesterone, m.p. 173–175°, but gave no optical rotation or details of its synthesis.

(3) H. Levy and M. L. Mednick (private communication) have independently isolated 4-hydroxyprogesterone as a by-product from the reaction of progesterone with hydrogen peroxide and osmium tetroxide and also by the acid dehydration of the 4,5-diol.

(4) The hypothesis is that formation of the 4,5-epoxide is followed by an "anomalous" opening of the oxide involving a C_{11} hydrogen. The possibility of this type of opening is suggested by the work of A. C. Cope, S. W. Fenton, and C. F. Spencer [*J. Am. Chem. Soc.*, 74, 5884 (1952)]. The resulting 4,11-dihydroxy compound then dehydrates to give the 3-keto-Δ^4-11-hydroxy compound.

(5) (a) B. Camerino, B. Patelli, and A. Vercellone have recently [*J. Am. Chem. Soc.*, 78, 3540 (1956)] described the epoxides from testosterone and the cleavage products from these oxides. (b) Since the completion of our work other groups have reported on overlapping work. See B. Camerino and B. Patelli, *Il Farmaco* (Pavia), *Ed. sci.*, 11, 579 (1956); B. Camerino, B. Patelli, A. Vercellone, and F. Media, *Il Farmaco* (Pavia), *Ed. sci.*, 11, 586 (1956); and H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, 21, 1432 (1956).

(6) Pl. A. Plattner, H. Heusser, and A. B. Kulkarni, *Helv. Chim. Acta*, 31, 1822 (1948).