4 hr. with 100% formic acid, and after boiling for 4 hr. with potassium hydroxide in ethanol and in 2-ethoxyethanol.

Further oxidation of dihydro-Compound-E_1. Dihydro-Compound-E_1 (1 g.) in acetic acid (30 ml.) was oxidized with a solution of chromium trioxide (0.4 g.) in 90% acetic acid (4 ml.). The product was precipitated with water and recrystallized from ethanol, when 0.4 g. of *dihydro-Compound-E_2* (XI) was obtained as white prisms, m.p. 224°, $[\alpha]_D^{20}$ +304° ($CHCl_3$, c. 0.60).

Anal. Calcd. for $C_{25}H_{26}O_7$: C, 68.5; H, 6.0. Found: C, 68.5; H, 6.0.

The *2,4-dinitrophenylhydrazone* was obtained as red needles, m.p. 261° on recrystallization from a mixture of ethanol and chloroform.

Anal. Calcd. for $C_{31}H_{30}O_{10}N_4$: C, 60.2; H, 4.9; N, 9.1. Found: C, 59.9; H, 4.7; N, 8.9.

ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. LXXXV.[1] Synthesis of 4-Methyl and 4,4-Dimethyl Hormone Analogs[2]

H. J. RINGOLD AND G. ROSENKRANZ

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4,4-Dimethyl-Δ^5-androsten-3-one derivatives have been prepared by alkylation of testosterone and 17α-methyltestosterone. The dihydroallo compounds are derived by catalytic hydrogenation of the Δ^5-3-ones while the corresponding 3β,17β-diols are obtained by borohydride reduction of the saturated and unsaturated ketones. Evidence is presented for the stereochemical course of catalytic and of hydride reduction, and molecular rotation discrepancies are discussed. 4-Methyltestosterone has been synthesized by alkaline cyclization of the reaction product of ethyl Grignard reagent and the enol lactone derived from ozonolysis of testosterone.

While the 4,4-dimethyl moiety is common in the triterpene series (*e.g.* lanosterol, euphol and β-amyrin) the only such steroidal compounds known have been just recently synthesized in the cholesterol[3] and ergosterol[4] series. As part of a broad program directed towards the correlation of steroid structure with activity we have had occasion to prepare a number of novel 4,4-dimethyl substituted androgen analogs as well as 4-methyltestosterone.

Treatment of testosterone (Ia) and 17α-methyltestosterone (Ib) with excess potassium *tert*-butoxide and methyl iodide in *tert*-butanol for several hours at room temperature[5] led in *ca.* 70% yield to 4,4-dimethyl-Δ^5-androsten-17β-ol-3-one (IIa) and to 4,4,17-trimethyl-Δ^5-androsten-17β-ol-3-one (IIb). These unsaturated ketones, in methanol solution, were smoothly hydrogenated at 25° and atmospheric pressure over a palladium-carbon catalyst to the corresponding dihydroallo derivatives, 4,4-dimethyldihydrotestosterone (IIIa) and 4,4,17-trimethyldihydrotestosterone (IIIb). Sodium borohydride reduction of the Δ^5-3-ketones (IIa and IIb) and of the 3-keto dihydro compounds (IIIa and IIIb) led in high yield to the respective Δ^5-3β-ols (IVa and IVb) and to the saturated 3β-ols (Va and Vb). Alternately, the saturated alcohol Va was prepared by catalytic hydrogenation of 4,4-dimethyl-Δ^5-androstene-3β,17β-diol (IVa), establishing that, as one would expect, reduction of the 5,6-double bond followed the same stereochemical course in the case of both the 3-ketone and the 3β-alcohol and further, hydride reduction of the 3-ketone led to the 3β-ol in the saturated as well as the unsaturated series.

Although, to our knowledge, there are no literature reports of the double bond hydrogenation of a steroidal Δ^5-3-ketone, the rings A/B *trans* configuration may be assigned to compounds III and V with certainty based on the following considerations: (1) catalyst absorption on the α-face of C-5,6 (which would lead to the A/B *trans* compound) is not sterically hindered, while the combination of a C-4β-axial methyl and a C-10 angular methyl group markedly hinders β-face approach to C-5,6; (2) the rotatory dispersion curves of IIIa and IIIb are identical with those of authentic 4,4-dimethyl-3-keto-A/B *trans* terpenes;[6] and (3) in all cases hydrogenation of a steroid Δ^5-3β-alcohol leads to the A/B *trans* compound.[7] That the alcohols IV and V are indeed the 3β (equatorial) alcohols follows from the recorded[3] lithium alumi-

(1) Paper LXXXIV, H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(2) Presented at the 129th Meeting of the American Chemical Society, Dallas, Tex., April 1956.

(3) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Am. Chem. Soc.*, **76**, 2852 (1954).

(4) G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 2998 (1955).

(5) These reaction conditions are those reported by Woodward, Barton, and co-workers, reference 3, in their elegant conversion of cholesterol to lanosterol.

(6) We are grateful to Professor C. Djerassi for the determination of rotatory dispersion curves of these compounds. For a description of this useful technique, see C. Djerassi, E. W. Folz, and A. E. Lippman, *J. Am. Chem. Soc.*, **77**, 4354 (1955).

(7) *e.g.* The hydrogenation of cholesterol leads exclusively to cholestanol [R. Willstätter and E. W. Mayer, *Ber.*, **41**, 2199 (1908)], and that of dehydroepiandrosterone to androstan-3β-ol-17-one [A. Butenandt, H. Dannenberg, G. Hanisch, and H. Kudszus, *Z. physiol. Chem.*, **237**, 57 (1935)].

num hydride reduction of the cholesterol series analog, 4,4-dimethyl-Δ^5-cholesten-3-one to the 3β-ol; arguing strictly from the steric viewpoint, hydride attack on the C-3 carbonyl from the β-face, which would be necessary for 3α-ol formation, is prevented in the compounds with or without a C-5 double bond by the steric interference of the C-4β-methyl group. Acceptance of the A/B *trans* configuration for III further necessitates the 3β-alcohol configuration for IV and V in view of the stereospecific hydride reduction of 4,4-dimethyl-3-keto-A/B *trans* terpenes to the 3β-alcohols.[8]

mal. Compounds III, with the greatest molecular rotation contributions, exhibit marked interaction between the 4β-methyl and C-10 angular methyl groups. The alcohols IV and V, with intermediate ΔM_D, do not show methyl-methyl interference, but in each case free rotation of the 3β-hydroxyl group is restricted by the 4β-methyl group, and further, in compound V, the 4β-methyl and the C-6-methylene groups are in severe interaction. Thus it would appear that in this series molecular rotation discrepancies may be correlated to steric interference factors with a fair degree of success.

TABLE I

MOLECULAR ROTATION DIFFERENCES OF 4,4-DIMETHYL STEROIDS

Substance	$[M]_D$	ΔM_D (parent compound)	
Δ^5-Cholestenone[a,b]	−10		
4,4-Dimethyl-Δ^5-cholestenone[b,c]	+4	+14	
Δ^5-Androsten-17β-ol-3-one acetate[d]	−101		Δ^5-3-Ketone
4,4-Dimethyl-Δ^5-androsten-17β-ol-3-one acetate (IIa acetate)	−104	−3	
Androstan-17β-ol-3-one[e]	+93		
4,4-Dimethylandrostan-17β-ol-3-one (IIIa)	−38	−131	Saturated 3-Ketone
17α-Methylandrostan-17β-ol-3-one[f]	+18		
4,4,17α-Trimethylandrostan-17β-ol-3-one (IIIb)	−116	−134	
Cholesterol[b,g]	−152		
4,4-Dimethylcholesterol[b,c]	−265	−113	
Δ^5-Androstene-3β,17β-diol[e]	−145		Δ^5-3β,17β-diol
4,4-Dimethyl-Δ^5-androstene-3β,17β-diol (IVa)	−261	−116	
17α-Methyl-Δ^5-androstene-3β,17β-diol[h]	−222		
4,4,17α-Trimethyl-Δ^5-androstene-3β,17β-diol (IVb)	−332	−110	
Androstane-3β,17β-diol[e]	+12		
4,4-Dimethylandrostane-3β,17β-diol (Va)	−51	−63	Saturated 3β,17β-diol
17α-Methylandrostane-3β,17β-diol[f]	−31		
4,4,17α-Trimethylandrostane-3β,17β-diol (Vb)	−94	−63	

[a] L. Fieser, *J. Am. Chem. Soc.*, **75**, 5421 (1953). [b] Rotation determined in chloroform (all others are in ethanol solution). [c] Reference 3. [d] H. Butenandt and G. Hanisch, *Ber.*, **69**, 2773 (1936). [e] Reference 13, p. 375. [f] Determined in these laboratories. [g] R. Anderson, *J. Biol. Chem.*, **71**, 407 (1926–27). [h] K. Miescher and W. Klarer, *Helv. Chim. Acta*, **22**, 962 (1939).

Inspection of molecular rotation differences (Table I) indicates a striking agreement in the cholestane, androstane and 17α-methylandrostane series. However, the rotatory contribution of a 4,4-dimethyl grouping is by no means constant. While the ΔM_D in going from the Δ^5-3-ketones to the corresponding 4,4-dimethyl compounds (II) is practically nil (+14 in the cholestene and −3 in the androstene series), the 4,4-dimethyl contribution rises to a value of about −60 in the saturated 3β-alcohols (Va and Vb), −110 in the Δ^5-3β-ol case (IVa, IVb and 4,4-dimethylcholesterol) and −130 in the 3-keto dihydroallo cases (IIIa and IIIb).

Inspection of molecular models reveals that only in the case of the 4,4-dimethyl-Δ^5-3-ketones (II) there is no steric interference of the 4β-methyl group with other groups in ring A; in these compounds the ΔM_D of the 4,4-dimethyl group is mini-

Efforts to prepare 4-methyltestosterone (IX) by modification of the direct methylation of testosterone were unrewarding and only trace amounts of the desired 4-monomethyl derivative were isolated. Compound IX was prepared in reasonable over-all yield (*ca.* 20% from testosterone) by the following reaction sequence.[9,10] Keto-acid VI from the ozonization of testosterone,[11a,b] was converted to the enol lactone (VII)[12] by heating with acetic anhydride and sodium acetate. Addition of ethyl Grignard reagent to the enol lactone followed by alkaline cyclization of the presumed intermediate VIII

(8) *Inter al.* "Reduction of Polyporenic Acid C", A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953); "Pinicolic Acid A," J. Guider, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 4471 (1954); "Methyl Dihydroelemolate," T. G. Halsall, G. D. Meakins, and R. Swayne, *J. Chem. Soc.*, 4139 (1953).

(9) This reaction scheme is one that was utilized by Professor E. R. H. Jones in the preparation of 4-methylcholestenone (private communication). We are grateful to Professor Jones for having provided us with a copy of his experimental details.

(10) F. Sondheimer and Y. Mazur (private communication from Dr. F. Sondheimer) have independently synthesized 4-methylcholestenone, testosterone, and progesterone, by this identical series of reactions.

(11) (a) C. C. Bolt, *Rec. trav. chim.*, **57**, 905 (1938); (b) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954).

(12) G. I. Fujimoto, *J. Am. Chem. Soc.*, **73**, 1856 (1951).

gave 4-methyltestosterone (IX). The ultraviolet absorption maximum of IX at 250 mμ is in good agreement with the predicted[13] 10-mμ bathochromic shift for an α-alkyl substituent on an α,β-unsaturated keto system.

In preliminary assays[14] in the immature castrate rat, 4-methyltestosterone, by the subcutaneous route, exhibited 40% of the androgenic and 120% of the myotrophic activity of testosterone.

EXPERIMENTAL[15]

4,4-Dimethyl-Δ⁵-androsten-17β-ol-3-one (IIa). To the solution of potassium *tert*-butoxide prepared from 8 g. of potassium and 400 cc. of *tert*-butanol, 20 g. of testosterone (Ia) was added under nitrogen and the mixture stirred until the steroid had dissolved. Methyl iodide (26 ml.) was added over a period of 10 min. to the yellow solution and the reaction vessel was stoppered under nitrogen and allowed to stand for 4 hr. without external cooling or heating. Water (300 cc.) was added, the *tert*-butanol removed *in vacuo* and the resultant crystalline suspension cooled and filtered. Recrystallization from acetone furnished 15 g. (68%) of pure IIa, m.p. 198–201°, $[\alpha]_D$ −10°, no highly selective ultraviolet absorption; infrared carbonyl absorption at 1700 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.67; H, 10.19. Found: C, 80.05; H, 10.28.

The acetate of IIa (acetic anhydride–pyridine, recrystallization from methanol) exhibited m.p. 154–156°, $[\alpha]_D$ −29°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.00; H, 9.34.

4,4,17-Trimethyl-Δ⁵-androsten-17β-ol-3-one (IIb). Methyltestosterone (Ia) when treated exactly as above gave the 4,4-dimethyl compound IIb in 78% yield, m.p. 194–196°, $[\alpha]_D$ − 32°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.94; H, 10.36. Found: C, 80.05; H, 10.57.

4,4-Dimethylandrostan-17β-ol-3-one (IIIa). The unsaturated ketone IIa (1 g.), in 30 cc. of methanol was hydrogenated at 25° and 1 atmosphere pressure over 500 mg. of prehydrogenated 10% palladium-carbon catalyst. Hydrogen uptake ceased in 4.5 hr. after the absorption of 92 cc. (theoret. 99 cc.), the filtered solution was taken to dryness and the residue crystallized from acetone-hexane to yield 0.82 g. of 4,4-dimethyldihydrotestosterone (IIIa), m.p. 140–146°. The analytical sample, from the same solvent, melted at 145–147°, $[\alpha]_D$ −12°, infrared carbonyl maximum at 1700 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.97; H, 10.69.

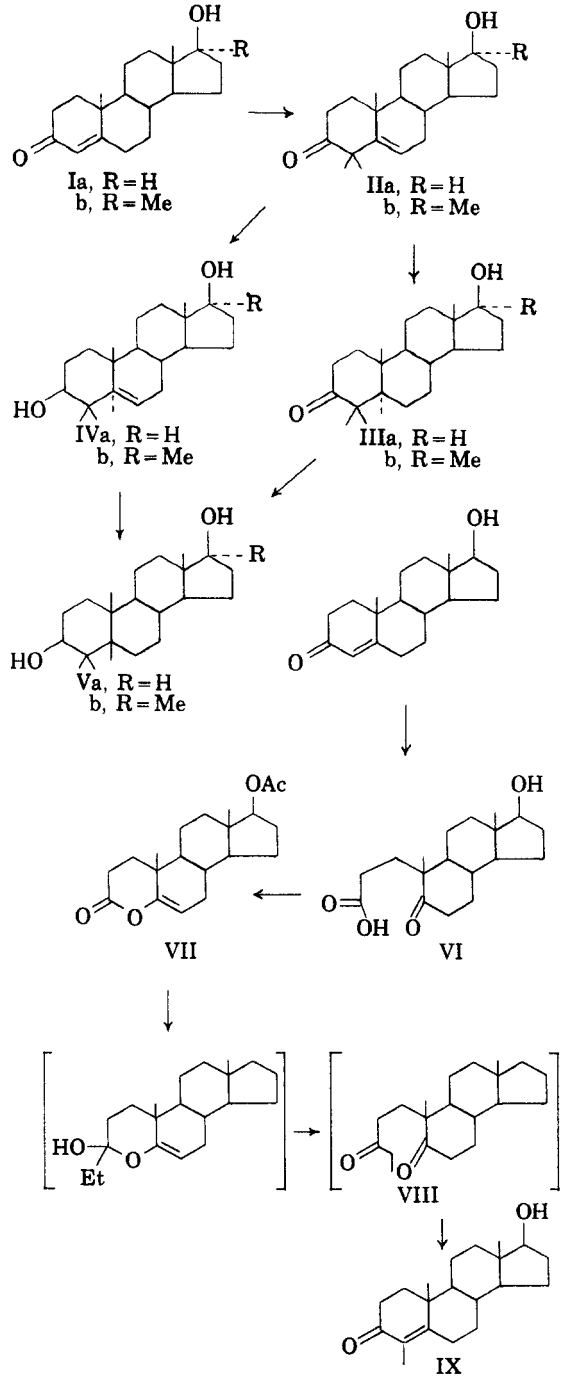
4,4,17-Trimethylandrostan-17β-ol-3-one (IIIb). Hydrogenation of 1 g. of IIIa as above (97 cc. hydrogen uptake in 5.5 hr.) and crystallization from acetone gave 600 mg. of 4,4,17-trimethyldihydrotestosterone (IIIb), m.p. 183–185°, $[\alpha]_D$ −35°.

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.75; H, 11.05.

4,4-Dimethyl-Δ⁵-androstene-3β,17β-diol (IVa). A solution of 1 g. of sodium borohydride in 2.5 cc. of water was added to 2 g. of IIa in 40 cc. of tetrahydrofuran, the mixture boiled for 1 hr. and the solvent finally removed *in vacuo*. Cold water (25 cc.) was added, the excess hydride decomposed by dropwise addition of glacial acetic acid (2 cc.), the crude IVa filtered, thoroughly washed with water, dried, and recrystallized from acetone, yielding 1.8 g. of 4,4-dimethyl-Δ⁵-androstene-3β,17β-diol, m.p. 213–217°. The analytical sample from acetone exhibited m.p. 216–218°, $[\alpha]_D$ −82°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.99; H, 10.48.

4,4,17-Trimethyl-Δ⁵-androstene-3β,17β-diol (IVb). Sodium borohydride reduction of IIb as described above for IIa gave a 90% yield of 4,4,17-trimethyl-Δ⁵-androstene-3β,17β-diol (IVb), m.p. 212–217°. Analytical sample (acetone), m.p. 216–220°, $[\alpha]_D$ −100°.



(13) See L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Third Edition, Reinhold Publishing Corp., New York, N. Y., 1949, pp. 190–192.

(14) Bioassays by the Endocrine Laboratories, Madison, Wis.

(15) Melting points are uncorrected. Unless specified otherwise, rotations and ultraviolet absorption spectra were determined in ethanol and infrared spectra in chloroform solution. Thanks are due Mrs. E. Necoechea and A. Mijares for their able technical assistance and to A. Erlin for determination of rotations and spectra.

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).