Hydrolysis of the Compounds.—The release of inorganic phosphorus from the four phosphorylated compounds of the vitamin B_6 series under various conditions is briefly outlined in Table III. Although pyridoxal phosphate was the most labile of the four, only 2% of its total phosphorus was detected as inorganic phosphorus after 54 days storage of an aqueous solution in a refrigerator or a freezer. In agreement with observations based on biological growth data[48] pyridoxal phosphate was more acid labile than pyridoxamine phosphate. Storage at room temperature for 54 days in 1 *N* HCl resulted in only 9% hydrolysis of the phosphate linkage in pyridoxal phosphate and only about 1% for the other compounds. In 1 *N* NaOH on the other hand pyridoxal phosphate appeared to be more stable.

(48) J. C. Rabinowitz and E. E. Snell, *J. Biol. Chem.*, **169**, 643 (1947).

At 100°, the difference between alkaline and acid hydrolysis was most evident (see Table III). In acid, the phosphoric ester bond was least resistant to hydrolysis in pyridoxal phosphate and most resistant in deoxypyridoxine phosphate. In alkali, on the other hand, although the ester bond in general was much more resistant to hydrolysis, pyridoxal phosphate was one of the more stable compounds. Pyridoxal and pyridoxamine phosphates were more rapidly hydrolyzed in dilute than in concentrated acid; none showed increased lability in dilute alkali. The last line in the table presents an estimate of the half lives of these compounds in 6 *N* sulfuric acid at 100°. Complete hydrolysis was obtained under these conditions in about 30 and 55 hours for the pyridoxal and pyridoxamine phosphates, respectively.

We are grateful to R. J. Koegel and his staff for the analyses presented in this paper.

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

The Stereochemistry of α-Haloketones. V. Prediction of the Stereochemistry of α-Brominated Ketosteroids

BY ELIAS J. COREY

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Methods are presented for predicting the orientation of bromine in all α-bromoketosteroids with ketone function in ring A, B or C and A/B *cis* or *trans*. One method applies to α-bromoketosteroids whose stereochemistry is thermodynamically controlled and the other method applies to α-bromoketosteroids whose stereochemistry is kinetically controlled. In every case there is agreement between predicted and determined configuration at $C_{(Br)}$. A number of cases are reported in which prediction has led to a redetermination and eventual reassignment of configuration. In other cases, configurations, which are consistent with predictions, are assigned for the first time using both infrared and chemical evidence. Thus it has been shown, in accord with expectation, that the bromination of 5α,6β-dibromocholestane-3-one produces the 4α-derivative faster than the 4β-derivative although the latter is the more stable. Likewise the bromination of 3α-acetoxycholestane-6-one affords, as predicted, the 5α-bromo derivative which is isomerized to the 7α-bromo derivative by hydrogen bromide. The assignment of α-orientation to the bromine in the latter substance, which conflicts with previous reports, has been proven by infrared absorption and transformation of the bromoketone to 3β-acetoxy-6β-hydroxy-7α-bromocholestane and thence to 3β-hydroxy-6,7β-oxidocholestane. The stereochemistry of the oxide was proved by reduction with lithium aluminum hydride to 3β,6β-dihydroxycholestane. The 5,7-dibromo derivatives of 3α-acetoxycholestane-6-one, m.p. 152° and m.p. 129°, have been shown to be, respectively, the 5α,7α- and 5α,7β-bromoketones. The product of bromination of methyl 3α,12α-diacetoxy-7-ketocholanate under conditions of thermodynamic control is the 6α-bromo epimer and not the β-epimer as previously reported.

Although the chemistry of α-bromoketosteroids has been the subject of much research, there have appeared no rules or methods for predicting whether the bromination of a given ketosteroid will lead to that epimer in which bromine is α-oriented, that in which bromine is β-oriented or a mixture of the two. Furthermore, as is now known, there are several instances in which the assignment of configuration to a bromoketosteroid, even after preparation and chemical study, has been incorrect. Another point of difficulty is the lack of distinction in the literature between thermodynamic (equilibrium) control of reaction product and kinetic (rate) control of reaction product. Such a distinction is important here because it may be possible for the primary bromination product (or products) to undergo thermodynamic equilibration by enolization. There are just a few cases in the literature where it is clear whether the bromoketone described is the stable or the unstable epimer. Obviously, any general method for predicting the stereochemistry of α-brominated ketosteroids must provide for both the thermodynamically and kinetically controlled products.

Recently, we have described in brief a method for deducing the more stable orientation of bromine in a bromoketosteroid.[1] This in turn gives the orientation which will occur in the thermodynamically controlled bromination product. In addition a rule has been proposed for predicting the stereochemistry of the kinetically controlled bromination product of a ketosteroid.[1] The present paper is concerned with the details of the application of these methods to specific α-bromoketosteroids.[2]

Thermodynamically Controlled Bromination Products.—It has been shown previously[3] that in the case of an α-bromocyclohexanone electrical repulsions involving carbon–oxygen and carbon–bromine dipoles destabilize the bromine-equatorial form relative to the bromine-polar form. On the

(1) E. J. Corey, *Experientia*, **9**, 329 (1953).

(2) The case of 2α-bromocholestane-3-one has already been discussed; E. J. Corey, THIS JOURNAL, **75**, 4832 (1953).

(3) E. J. Corey, *ibid.*, **75**, 2301 (1953).

other hand, steric repulsions, which are at a maximum when bromine is polar, destabilize the bromine-polar form. As a result, in some cases the stable form is that in which bromine is polar, while in others it is that in which bromine is equatorial. Since the electrical repulsions are relatively constant, the magnitude of the steric repulsions involving polar bromine will determine the stereochemistry of the stable form.

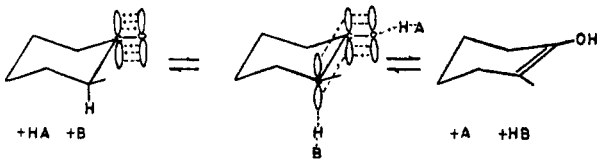


Fig. 1.

The relative importance of electrical and steric destabilizations for a given set of substituents can be determined by a study of the preferred molecular configuration of an appropriately substituted monocyclic α-bromocyclohexanone which is free to adopt the chair form with bromine equatorial or that with bromine polar. Fortunately, a relatively small number of monocyclic reference substances are needed to determine the relative importance of the interactions in α-bromo- and α,α'-dibromoketosteroids. These are listed together with the preferred molecular configurations in Table I. From these data one can derive the relative stabilities of the epimeric bromination products of any ketosteroid with ketone function in ring A, B or C and A/B *cis* or *trans*. The results are indicated in Table II.

TABLE I

RELATIVE STABILITIES OF CHAIR-FORMED CONFORMATIONS OF α-BROMOCYCLOHEXANONES

Ketone	Approx. $K_{eq.}$, $\frac{[\text{Br polar}]^a}{[\text{Br equatorial}]}$
2-Bromocyclohexanone-1[3]	>50
2-Bromo-3,3-dimethylcyclohexanone-1[4]	>40
2-Bromo-4,4-dimethylcyclohexanone-1[3]	<0.01
2-Bromo-6,6-dimethylcyclohexanone-1[4]	~0.4
7-Bromo-spiro[4.5]decane-6-one[3]	~0.4
cis-2,6-Dibromocyclohexanone-1[5,b]	<0.05

[a] In carbon tetrachloride at 25°. Data obtained by infrared spectroscopy. [b] In addition it should be noted that for *cis*- and *trans*-2,6-dibromocyclohexanone $K_{trans/cis} \cong 5.6$.[5]

TABLE II

STABILITY OF EPIMERIC α-BROMOKETOSTEROIDS

A/B *trans*		A/B *cis*	
Position of ketone function	Configuration of Br in stable epimer	Position of ketone function	Config. of Br in stable epimer
$C_{(1)}$	$C_{(2)}$:α (e)[a]	$C_{(1)}$	$C_{(2)}$:β (e)[a]
$C_{(2)}$	$C_{(1)}$:α (p) $C_{(3)}$:α (p)	$C_{(2)}$	$C_{(1)}$:β (p) $C_{(3)}$:β (p)
$C_{(3)}$	$C_{(2)}$:α (e) $C_{(4)}$:α (e)	$C_{(3)}$	$C_{(2)}$:β (e) $C_{(4)}$:β (e)
$C_{(4)}$	$C_{(3)}$:α (p) $C_{(5)}$:α (p)	$C_{(4)}$	$C_{(3)}$:β (p) $C_{(5)}$:α (p)
$C_{(6)}$	$C_{(5)}$:α (p) $C_{(7)}$:α (p)	$C_{(6)}$	$C_{(5)}$:α (p) $C_{(7)}$:β (e)
$C_{(7)}$	$C_{(6)}$:α (e) $C_{(8)}$:β (p)	$C_{(7)}$	$C_{(6)}$:α (e) $C_{(8)}$:β (p)
$C_{(11)}$	$C_{(9)}$:α (p) $C_{(12)}$:α (p)	$C_{(11)}$	$C_{(9)}$:α (p) $C_{(12)}$:α (p)
$C_{(12)}$	$C_{(11)}$:α (e)	$C_{(12)}$	$C_{(11)}$:α

[a] The isomer with bromine polar should be only slightly less stable and the equilibrium mixture of $C_{(2)}$ epimers should contain *ca.* 75% of the epimer with bromine equatorial and 25% of the epimer with bromine polar.

The Kinetically Controlled Bromination Products.—The rule which has been developed for predicting the stereochemistry of the kinetically controlled bromination products of bromoketosteroids is as follows: *the epimer which is formed faster in the bromination of a ketosteroid is that in which bromine is polar.*

A better understanding of the rule may be had by considering the theoretical basis upon which it was derived. Ketonization of an enol and the reverse reaction, enolization of a ketone proceed through the same transition state and hence the same geometrical requirements for minimizing the energy of the transition state hold for both reactions. The energy of the transition state for enolization will be at a minimum when there is maximum opportunity for bond formation between the $sp^3 \rightarrow$ p orbital made available by the leaving hydrogen and the p orbital of the carbonyl carbon.

In the case of a cyclohexanone this implies that in enolization a polar α-hydrogen is lost in preference to an equatorial α-hydrogen. Furthermore, it follows that in the ketonization of an enolized cyclohexanone (*e.g.*, by bromination or protonation) the incoming substituent should adopt preferentially the polar orientation (see Fig. 1).

Comparison of Predicted and Determined Configurations of α-Bromoketosteroids. A-Ring Ketones.—The only reported monobromo derivatives of A-ring ketones are those of the 3-ketones in the normal and allo series. It has been shown previously[2] that the 2-bromocholestane-3-one which is produced by bromination of cholestane-3-one is not subject to epimerization under equilibrating conditions (hydrogen bromide–acetic acid) and is the 2α-epimer. This agrees with the configuration predicted for the stable epimer (Table II). Likewise the bromination of coprostane-3-one produces a 4-bromo derivative[6] which cannot be epimerized. Here again the predicted and determined[7,8] orientation of bromine (β) are in accord.

Butenandt and co-workers[9,10] reported that the bromination of 5α,6β-dibromocholestane-3-one[11] in acetic acid produces a 4-bromo derivative, m.p. 106°, while Inhoffen[12] in the same year reported that the bromination of the same ketone in ether–acetic acid produces a 4-bromo derivative, m.p. 138°. We have been able to duplicate the result

(4) E. J. Corey and T. Topie, to be published.

(5) E. J. Corey, THIS JOURNAL, **75**, 3297 (1953).

(6) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

(7) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952).

(8) L. F. Fieser and R. Ettore, *ibid.*, **75**, 1700 (1953).

(9) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **69**, 882 (1936).

(10) A. Butenandt and G. Schramm, *ibid.*, **69**, 2289 (1936).

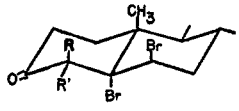
(11) For the configurations at $C_{(5)}$ and $C_{(6)}$ see D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).

(12) H. H. Inhoffen, *Ber.*, **69**, 1134, 1702, 2111 (1936).

of Butenandt without difficulty, but have not been able to duplicate those of Inhoffen. The many runs which were carried out under the conditions described by Inhoffen afforded, in our hands, good yields of the Butenandt bromoketone, m.p. 106°, and no isolable Inhoffen bromoketone, m.p. 138°. However, we were able to obtain the bromoketone, m.p. 138°, in good yield by isomerization of the bromoketone, m.p. 106°, with ethereal hydrogen chloride. Inhoffen's substance, m.p. 138°, is therefore the stable epimer and the product of thermodynamic control, while the Butenandt bromoketone m.p. 106° is the unstable epimer and the product of kinetic control.

From these data one would predict that Inhoffen's compound m.p. 138° is the 4α,5α,6β-tribromoketone and that Butenandt's compound, m.p. 106°, is the 4β,5α,6β-tribromoketone. These assignments coincide with the stereochemistry of these substances as determined by infrared spectroscopy using the method of Jones, *et al.*,[7] and as indicated by their chemical reactivity.

The shift in frequency of carbonyl absorption (Δ) in going from 5α,6β-dibromocholestane-3-one (I) to the Inhoffen bromoketone, m.p. 138°, (II) is 18 cm.$^{-1}$ (Table III) which indicates that bromine is equatorial (α). The shift in carbonyl absorption in going from I to the Butenandt bromoketone, m.p. 106°, (III) is only 4 cm.$^{-1}$ which indicates that bromine is polar (β). These assignments are supported



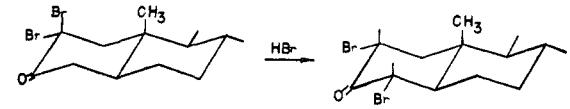
I, R = R′ = H
II, R = H, R′ = Br
III, R = Br, R′ = H

by the observation that the Inhoffen bromoketone can be dehydrobrominated to 4,6β-dibromo-Δ^4-cholestene-3-one by means of potassium acetate in alcohol under conditions which do not affect the Butenandt tribromide.

TABLE III

Bromoketone	Position of ketone C=O absorption, cm.$^{-1}$	Shift due to α-bromine, Δ cm.$^{-1}$
5α,6β-Dibromocholestane-3-one (I)	1720	...
4α,5α,6β-Tribromocholestane-3-one (m.p. 138°)	1738	18
4β,5α,6β-Tribromocholestane-3-one (m.p. 106°)	1724	4
3β-Acetoxycholestane-6-one	1711	...
3β-Acetoxy-5α-bromocholestane-6-one	1711	0
3β-Acetoxy-7α-bromocholestane-6-one	1713	2
3β-Acetoxy-5α,7α-dibromocholestane-6-one	1708	−3
3β-Acetoxy-5α,7β-dibromocholestane-6-one	1727	16
Methyl 3α,12α-diacetoxy-7-ketocholanate	1717	...
Methyl 3α,12α-diacetoxy-6α-bromo-7-ketocholanate	1737	20

The dibromination of cholestane-3-one yields the 2,2-dibromo derivative IV which when treated with hydrogen bromide is isomerized to a stable 2,4-dibromocholestane-3-one.[13,14] The predicted and determined[7] stereochemistry of this stable 2,4-dibromoketone coincide and indicate that both bromine substituents are α-oriented as shown in formula V. It is noteworthy that the isomerization of the 2,2-dibromide IV to the 2,4-dibromide V is also in accord with prediction. Likewise both

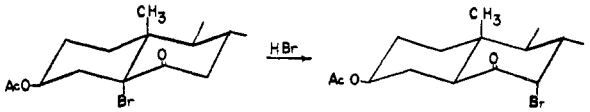


IV V

experiment and theory indicate that the stable form of the known 2,4-dibromocoprostane-3-one[15,16] is that which possesses β-oriented (equatorial) bromine substituents.[7]

B-Ring Ketones.—The bromination of 3β-acetoxycholestane-6-one affords a 5-bromo derivative, m.p. 162°, of unassigned configuration.[17] Clearly, this product is that corresponding to kinetic control, since epimerization at $C_{(5)}$ by enolization is not possible, and would be expected to have the α-configuration (polar Br). We have prepared this substance and have determined by infrared absorption that the 5-bromine is indeed α-oriented (Δ = 0).

Prolonged treatment of 3β-acetoxy-5α-bromocholestane-6-one, m.p. 162°, (VI) with hydrogen bromide in acetic acid produces an isomeric 7-bromoketone, m.p. 145°, which has been designated recently as the 7β-bromo epimer,[18] because of its resistance to dehydrobromination. This assignment is contrary to expectation based on the considerations described above, since the product of thermodynamic control, which is undoubtedly operative under these conditions, is the 7α-bromoketone. Furthermore, the 7α-isomer is also the expected product of kinetic control. The infrared absorption of the bromoketone, m.p. 145°, (Table III, Δ = 2) clearly shows that the bromine at $C_{(7)}$ possesses the α-orientation (VII) and not the β-orientation as was previously assigned.[19]



VI VII

(13) H. H. Inhoffen, *Ber.*, **70**, 1695 (1937); H. H. Inhoffen and R. Zuhlsdorff, *ibid.*, **76**, 233 (1943).

(14) C. Djerassi and C. R. Scholz, THIS JOURNAL, **69**, 2404 (1947).

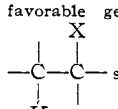
(15) L. Ruzicka, W. Bosshard, W. H. Fischer and H. Wirz, *Helv. Chim. Acta*, **19**, 1147 (1936).

(16) C. Djerassi and G. Rosenkranz, *Experientia*, **7**, 93 (1951).

(17) I. M. Heilbron, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 801 (1937).

(18) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y., p. 268.

(19) The reluctance of VII to undergo base-catalyzed elimination is quite unusual for substances such as VII which possess the most favorable geometry for β-elimination, *i.e.*, the *trans*, co-planar



system. This inertness might be due to shielding by the methyl groups at $C_{(10)}$ and $C_{(13)}$ which could prevent effective solvation of the transition state or possibly interact sterically with the base attacking the hydrogen at $C_{(9)}$.

Even though the infrared evidence in favor of structure VII for the bromoketone, m.p. 145°, seemed compelling, it was considered desirable to obtain conclusive chemical evidence on this point. This evidence, which completely supports the conclusions drawn from the infrared data, is as follows. Treatment of the bromoketone, m.p. 145°, with sodium borohydride in isopropyl alcohol afforded a mixture of products containing both possible bromohydrins. The mixture upon treatment with alkali furnished pure 3β-hydroxy-6,7β-oxidocholestane which was easily isolated by chromatography. The substance was proved to be the β-oxide by reduction with lithium aluminum hydride to the known cholestane-3β,6β-diol. Thus it is necessary to formulate the bromohydrin from which the oxide was formed as 7α-bromocholestane-3β,6β-diol and the original bromoketone, m.p. 145°, as 3β-acetoxy-7α-bromocholestane-6-one (VII).[20]

With the structure of the 3-acetoxy-7-bromocholestane-6-one, m.p. 145°, firmly established as VII and in view of the inertness of this compound in elimination reactions, it is of interest to examine other possible cases in which $C_{(7)}$,$C_{(8)}$-*trans*-elimination is abnormally slow. One such case appears to be the 3β-acetoxy-7-chlorocholestane which is produced by reaction of 3β-acetoxy-7β-hydroxycholestane with phosphorus oxychloride. This substance, in which the 7-chlorine is probably α-oriented, fails to undergo elimination in boiling pyridine.[21]

The dibromination of 3β-acetoxycholestane-6-one produces a dibromide of m.p. 152° which is isomerized to a dibromide of m.p. 129° under the influence of hydrogen bromide in acetic acid.[22] The dibromide, m.p. 152°, can also be produced by bromination of 5α- or 7α-bromo-3β-acetoxycholestane-6-one. Both bromides upon treatment with basic reagents are converted to Δ^4-cholestene 3,6-dione which indicates that they are 5,7- and not 7,7-dibromides. The orientation of bromine at $C_{(5)}$ in both bromides would be predicted to be α, since equilibration by enolization at this position is not possible and since bromination at $C_{(5)}$ should lead to the 5α-(polar) oriented bromine substituent. From this fact and the data on the dibromocyclohexanones in Table I, it follows that the unstable dibromide, m.p. 152°, must be the 5α,7α-(polar, polar) isomer and the stable dibromide, m.p. 129°, must be the 5α,7β-dibromide. These predictions are completely confirmed by the infrared absorption of these substances (Table III). The Δ value for the isomer m.p. 152° (Δ = −3) indicates that both bromines are polar (α) and the Δ value for the isomer m.p. 129° (Δ = 16) indicates that one bromine is polar (α) and one bromine is equatorial (β).

The bromination of 3β-acetoxycholestane-7-one yields a 6-bromo derivative, m.p. 175°, which is isomerized by treatment with hydrogen bromide to an epimeric 6-bromoketone, m.p. 143°.[23] The isomer, m.p. 175°, would be predicted to be the 6β-bromo isomer (Br polar) and the isomer, m.p. 143°, would be predicted to be the 6α-isomer (Br equatorial). These predictions agree with the unequivocal assignments of configuration which have already been made.[23]

The orientation of the 6-bromine in the bromination products of 7-ketosteroids of the normal series has been assumed to be β because of the resistance of these substances to dehydrobromination.[24-26] However, this assumption cannot be considered valid in view of the fact that neither the 6α- nor the 6β-epimer possesses the required geometry for facile elimination, *i.e.*, coplanarity of the four reacting centers. We have prepared a methyl 3α,12α-diacetoxy-6-bromo-7-ketocholanate, m.p. 165°, which cannot be epimerized, by bromination of the 7-ketone and have determined by the infrared method that, as predicted, the bromine atom is α-oriented (equatorial, Δ = 20). This product could be isolated only when the bromination mixture, which contained hydrogen bromide, was allowed to stand for 6 hours or longer. When the bromination product was worked up as soon as the bromination was completed, only amorphous material could be recovered. The infrared spectrum of this material showed that it consisted largely of the epimeric 6β-bromoketone (Br polar), since there was strong absorption at 1720–1725 cm.$^{-1}$ (Δ = 3 to 8). These findings are consistent with prediction.

C-Ring Ketones.—The bromination of an 11-ketosteroid at $C_{(12)}$ would be expected to yield the 12α-epimer, since this is the product predicted for both kinetic and thermodynamic control. This expectation is borne out by the finding that the bromination of methyl 11-keto-3α-acetoxycholanate and of other 11-ketosteroids produces only the 12α-isomer, which apparently is not subject to epimerization.[27,28]

In the case of a typical 12-ketosteroid, 12-keto-3α-acetoxycholanic acid, bromination under vigorous conditions has been reported to afford a mixture of 11α- and 11β-epimers in which the 11α-epimer predominates.[29,30] The 11α-epimer is that which would be predicted to be more stable and the 11β that which should be formed faster. We have found that the 11β-epimer can be isomerized under

(20) It is interesting to note that the reduction of the 6,7β-oxide provides another example of an oxide ring opening with lithium aluminum hydride in which the ring cleavage is stereospecific and occurs so as to produce a polar hydroxyl group; *cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953). It is evident from a comparison of the transition states for ring opening that the transition state in which the entering (nucleophilic) species (here $H\delta^-$) the displaced group (here O^-) and the carbon undergoing backside attack are most closely linear is that in which the entering and displaced group are becoming polar. This would account for the observed sterospecificity, since the energy of the transition state for a displacement reaction decreases with increasing colinearity of the reacting centers.

(21) For this reason L. F. Fieser, M. Fieser and R. N. Chakravati, THIS JOURNAL, **71**, 2226 (1949), have assigned the 7β-configuration of chlorine to this compound and have assumed that the reaction of the 7β-ol with phosphorus oxychloride proceeds with retention.

(22) I. M. Heilbron, H. Jackson, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 102 (1938).

(23) T. Barr, I. M. Heilbron, E. R. H. Jones and F. S. Spring, *ibid.*, 334 (1938).

(24) W. M. Hoehn and J. Linsk, THIS JOURNAL, **67**, 312 (1945).

(25) R. Grand and T. Reichstein, *Helv. Chim. Acta*, **28**, 344 (1945).

(26) A. Lardon, *ibid.*, **30**, 597 (1947).

(27) E. Borgstrom and T. F. Gallagher, *J. Biol. Chem.*, **162**, 707 (1946).

(28) V. R. Mattox, R. B. Turner, B. F. McKenzie, L. L. Engel and E. C. Kendall, *ibid.*, **173**, 283 (1948).

(29) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).

(30) T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, **162**, 495 (1946).

acidic conditions to the 11α-epimer which indicates that, as predicted, the 11α-epimer is more stable than the 11β-epimer and is probably formed from it during the bromination.

Experimental[31]

4β,5α,6β-Tribromocholestane-3-one (III).—5α,6β-Dibromocholestane-3-one (I) was prepared both by the method of Butenandt[10] and Inhoffen.[12] The former method afforded material of m.p. 79–80° and the latter material of m.p. 68–69° in agreement with the results reported.[10,12] The material m.p. 68–69° is less pure than that m.p. 79–80°, but undoubtedly consists mostly of the same substance (I) as is indicated by mixture melting point and infrared absorption. The tribromide III was prepared conveniently in the following manner. To a solution of 2.00 g. of the dibromoketone I in 40 ml. of ether at 10° was added a few drops of 10% hydrogen bromide in acetic acid and 0.60 g. of bromine in 10 ml. of acetic acid (dropwise). The ether was evaporated in the cold under reduced pressure and the colorless precipitate, was collected by filtration, washed with methanol and recrystallized from acetone–water. The yield of 4β,5α,6β-tribromocholestane-3-one, m.p. 106–106.3°, was 1.68 g. Recrystallization from ether–acetic acid or acetone–water did not change the m.p.

The same substance was isolated when the reaction was carried out in absolute ether, wet ether, chloroform or acetic acid at 0° or room temperature.

4α,5α,6β-Tribromocholestane-3-one (II).—A solution of 1.20 g. of 4β,5α,6β-tribromocholestane-3-one (III) in 30 ml. of ether saturated with hydrogen chloride was allowed to stand at room temperature for 4 hours. The ether was evaporated under reduced pressure and the residue recrystallized from acetic acid to give 0.693 g. of 4α,5α,6β-tribromocholestane-3-one (II), m.p. 138–138.5°. The infrared spectrum of this material showed that it contained a small amount (*ca.* 5%) of 4,6β-dibromo-Δ⁴-cholestane-3-one. Several recrystallizations afforded pure material, m.p. 139.5–140°.

Anal. Calcd. for $C_{27}H_{43}OBr_3$: C, 51.98; H, 6.95. Found: C, 51.75; H, 6.97.

Comparative Dehydrobromination of II and III.—Two experiments were carried out with II and III under the conditions described by Inhoffen[12] for the dehydrobromination of II except for a reaction time of 13 hours at room temperature. The 4α-epimer (II) gave a 47% yield 4,6β-dibromo-Δ⁴-cholestane-3-one, m.p. 162–163°, as described by Inhoffen,[12] and the 4β-epimer III was recovered unchanged in 71% yield.

Conversion of 3β-Acetoxy-7α-bromocholestane-6-one to 3β-Hydroxy-6,7β-oxidocholestane.—To a solution of 1.00 g. of 3β-acetoxy-7α-bromocholestane-6-one in 30 ml. of isopropyl alcohol was added a solution of 0.10 g. of sodium borohydride in 30 ml. of isopropyl alcohol. After standing at room temperature for one hour a solution of 3.0 g. of potassium hydroxide in 20 ml. of isopropyl alcohol was added and the solution was heated to 70° for 15 minutes. The solution was then concentrated to 10 ml. and diluted with water. The precipitate was collected, washed well with water and dried. The infrared spectrum of this material showed hydroxyl absorption and weak carbonyl absorption at 1710 cm.$^{-1}$ indicating the presence of some 3β-hydroxycholestane-6-one. The total reaction mixture was chromatographed on a column (250 × 18 mm.) of basic alumina. The first material to be eluted (with 5:1 benzene–ether) was 3β-hydroxy-6,7β-oxidocholestane, 273 mg., m.p. 156–158°. The oxide was purified for analysis by two recrystallizations from acetone–water, m.p. 157.5–158.5°, $[\alpha]_D$ −14.5° (*c* 1.38, chloroform). The oxide was found to be slightly hygroscopic.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.63; H, 11.59.

The infrared spectrum of the oxide showed hydroxyl absorption and no carbonyl absorption.

Lithium Aluminum Hydride Reduction of 3β-Hydroxy-6,7β-oxidocholestane.—A solution of 0.220 g. of 3β-hydroxy-6,7β-oxidocholestane in 40 ml. of ether was added to an ice-cold solution of 0.100 g. of lithium aluminum hydride in 40 ml. of ether and the solution allowed to stand for one hour. The excess hydride was decomposed with methanol and the ethereal solution was extracted with dilute sodium hydroxide, dried and evaporated to a solid residue. Recrystallization from alcohol–water afforded 0.190 g. of cholestane-3β,6β-diol, m.p. 189–190° alone or admixed with an authentic sample, m.p. 189–190°, prepared by the procedure of Plattner and Lang.[32] The infrared spectra of experimental and authentic samples were identical. Both materials yielded the same diacetate, m.p. 138–139°,[32] upon treatment with acetic anhydride–pyridine.

Methyl 3α,12α-Diacetoxy-6α-bromo-7-ketocholanate.—Methyl 3α,12α-diacetoxy-7-ketocholanate was prepared by the oxidation of methyl cholate with N-bromosuccinimide in aqueous acetone (4 g. of methyl cholate, 100 ml. of acetone, 40 ml. of water and 2.5 g. of N-bromosuccinimide; reaction time, 6 hours) and acetylation of the resulting crude product with hot acetic anhydride–acetic acid. To 0.150 g. of the diacetoxyketone, m.p. 118.0–118.4°, in 2.5 ml. of glacial acetic acid containing 3% hydrogen bromide was added a solution of 0.050 g. of bromine in one ml. of acetic acid. The reaction mixture was stored at room temperature for 12 hours and then poured into water. The solid was collected, washed with water and recrystallized from methanol–water at −5°. The yield of bromoketone, m.p. 164–165°, was 0.140 g. One recrystallization afforded pure material, m.p. 165–165.5°.

Anal. Calcd. for $C_{29}H_{43}O_7Br$: C, 59.69; H, 7.43; Br, 13.70. Found: C, 59.88; H, 7.59; Br, 13.56.

In a similar run in which the reaction was worked up as soon as the bromine had been taken up (8 minutes) the product was an amorphous solid which could not be crystallized. The infrared spectrum and the elementary analysis of this material (Found: Br, 13.40; infrared absorption between 1720 and 1725 cm.$^{-1}$) indicated that it consisted largely of the 6β-bromo epimer.

Preparation of Other α-Bromoketosteroids.—The preparation of 4β-bromocoprostane-3-one,[6] 2β,4β-dibromocoprostane-3-one,[15] 3β-acetoxy-5α- and 3β-acetoxy-7α-bromocholestane-6-one[17] and 3β-acetoxy-5α,7α- and 3β-acetoxy-5α,7β-dibromocholestane-6-one[22] was carried out essentially according to the published procedures. The epimeric 11-bromo-3α-acetoxy-12-ketocholanic acids and the corresponding methyl esters were prepared as described by Seebeck and Reichstein.[29] Equilibration experiments were carried out by allowing the bromoketone in acetic acid containing 3% hydrogen bromide to stand at room temperature for 6 hours in the case of the A-ring ketones and 12 hours or longer in the case of the B- and C-ring ketones.

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(32) Pl. A. Plattner and W. Lang, *Helv. Chim. Acta*, **27**, 1872 (1944),