between γ- and δ-lactone ring systems, but they are little influenced by the mode or position of attachment of the lactone group, and are not selective enough to distinguish among various types of lactones of the same ring size. No specific examples of the perturbation of these bands by other neighboring carbonyl groups have been encountered, though there is limited evidence to show that the lactone carbonyl frequency may be depressed by the hydroxyl group in the structure -CO-O-C(OH)- and elevated by the halogen in the structure -CO-O-C(Cl)-. In enol lactones of types XXXVI, XLII and XLIV the C=O frequency is raised. The C=O frequency range for enolic δ-lactones may overlap the range for γ-lactols of the type discussed above (*cf.* XV with XLII and XLIV) and caution must be used in evaluating the lactone ring size where the C=O frequency lies in the range between 1770 and 1755 cm.$^{-1}$. ε-Lactones may absorb at significantly lower frequencies than δ-lactones, but the available evidence is inconclusive.

The presence of two "carbonyl" bands associated with the $\Delta^{20(22)}$-cardenolide and $\Delta^{20,22}$-bufadienolide systems is unusual. The most plausible explanation is a Fermi type resonance between the true C=O stretching vibration and a second vibration, possibly an overtone of a low frequency fundamental. Such an hypothesis is difficult either to confirm or to refute; our investigations on simple butenolides and pyrones fully confirm the generality of the behavior but, as yet, have not provided a satisfactory explanation. Whatever the cause, this solvent effect offers a useful diagnostic method for the identification of such lactone ring systems in compounds of unknown structure. Where solubility conditions permit, this region of the spectrum should be routinely investigated in solvents of both low and high polarity.

The various types of saturated lactones show characteristic differences between 1500 and 1300 cm.$^{-1}$ though the α-methylene bands cannot be distinguished from similar bands of ketones and straight chain esters. The strong "C-O stretching bands" between 1250 and 1000 cm.$^{-1}$ are also sensitive to the type of lactone ring, but they are difficult to recognize where other functional groups are also present unless the curves for appropriate non-lactonic steroids are available for comparison purposes.

Acknowledgment.—The authors wish to thank the several investigators, listed individually in a footnote to Table I, who kindly made available many of the compounds. We are particularly grateful to Prof. T. Reichstein who provided the unique series of cardanolide and the bufanolide derivatives. We also wish to thank Dr. D. Fleischer of the Sloan-Kettering Institute and Dr. D. Taub of the Merck Laboratories for several valuable suggestions, and Mr. D. S. Keir, Mr. R. Lauzon and Mrs. M. A. Mackenzie for technical assistance with the measurement of the spectra.

This investigation was supported, in part, by a grant from the American Cancer Society and a research grant (CY3207) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

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Glycol Fission in Rigid Systems. II. The Cholestane-3β,6,7-triols. Existence of a Cyclic Intermediate[1]

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RECEIVED MARCH 6, 1959

The four diastereomeric cholestane-3β,6,7-triols have been synthesized and their configurations determined. Their rates of oxidation by lead tetraacetate, phenyl iodosoacetate and periodate have been measured; the 3β,6β,7α-isomer, which contains a diaxial glycol group, is not attacked by either reagent. The results support a mechanism for the glycol fission involving a cyclic intermediate (or transition state).

In the preceding paper[2] it has been shown that glycol fission is extremely slow when the projected valency angle (between the two C-OH bonds, viewed along the C-C axis) in a vicinal glycol is rigidly held at 120°. Subsequently it appeared desirable to investigate a case where the projected valency angle is rigidly held at 180°. Such an angle occurs, for example, between axial groups on vicinal carbon atoms in a cyclohexane ring; but to assure the rigidity of that angle the ring must be prevented from changing into other conformations. This can be achieved by *trans*-fusion to the ring of two other cyclohexane rings: ring B of cholestane is thus immobilized. A derivative of cholestane containing two axial hydroxyl groups at C6 and C7 was chosen for study and, to have a sound basis for comparison, its three diastereomers were also prepared and investigated. Cholesterol served as the starting material for their synthesis; hence the four glycols also had a 3β-hydroxyl group; its presence, however, has no effect on the glycol fission.

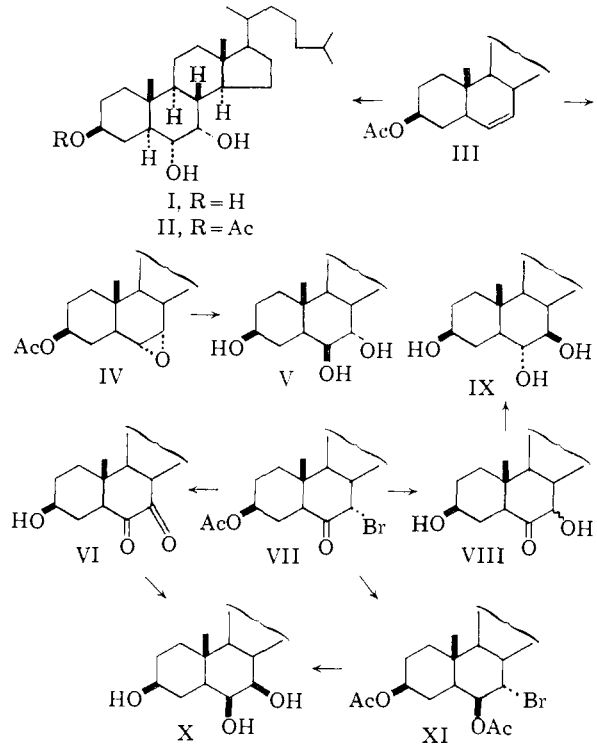
Wintersteiner and Moore[3] prepared the only previously known cholestane-3β,6,7-triol by hydroxylation of 3β-acetoxycholest-6-ene (III) with osmium tetroxide, but they did not assign a configuration to it. By nature of the reaction it must be a *cis*-glycol; and since hydroxylation of

(1) Abstracted from part of the Ph.D. Thesis of R. J. Young, Sydney, 1958.

(2) S. J. Angyal and R. J. Young, THIS JOURNAL, **81**, Oct. 20 (1959).

(3) O. Wintersteiner and M. Moore, *ibid.*, **72**, 1923 (1950).

unsaturated 5α-steroids generally occurs from the unhindered α-side,[4-7] it is probable that the compound is the 3β,6α,7α-triol I. In support of this assignment it is worth mentioning that the reaction of III with perbenzoic acid[8] gives an epoxide (IV) which has the α-configuration.



Acid hydrolysis of 3β-acetoxy-6α,7α-epoxycholestane[8] (IV) yielded an acetoxydiol which, on removal of the acetyl group, gave rise to a cholestanetriol. Since hydrolysis of steroidal epoxides yields diaxial glycols,[9-11] the 3β,6β,7α-triol configuration V has been assigned to this diastereomer.

Reduction of ketones with sodium and alcohol is known[10] to give predominantly the most stable diastereomer; therefore the triequatorial 3β,6α,7β-triol IX would be the expected product from the reduction of a corresponding hydroxyketone. One of these, a 3β,7-dihydroxycholestan-6-one (VIII), has been described by Heilbron, Jones and Spring[12] who prepared it by alkaline hydrolysis of 3β-acetoxy-7α-bromocholestan-6-one[12,13] (VII). In our hands, the reaction, however, gave a mixture from which 3β-hydroxycholestane-6,7-dione (VI) was isolated. The diketone presumably arose by aerial oxidation; a similar instance has been described by Takeda, Komeno and Igarashi.[14] When the reaction was carried out under nitrogen, the amount of diketone formed was considerably decreased, but the hydroxyketone had a variable melting point and rotation. Under the alkaline conditions of the reaction an enediol would be formed which could give rise to four isomeric hydroxyketones; the "3β,7-dihydroxycholestan-6-one" is therefore probably a mixture of isomers and it is by no means certain that the keto-group is located at C6. For reduction to a triol, however, it is immaterial which isomer is present; this reduction, carried out by sodium in 1-butanol, gave a new triol to which the 3β,6α,7β-configuration IX has been assigned.

Another triol was prepared by hydrogenation of 3β-hydroxycholestane-6,7-dione (VI) and of its acetate. Since the diketone would be adsorbed by the catalyst surface on the unhindered α-side, the addition of hydrogen would occur from that side and the triol would be expected to have the 3β,6β,7β-configuration X, the only one not yet assigned. The product of the hydrogenation was, in fact, different from the other three cholestane-3,6,7-triols and therefore has formula X.

Although this allocation of configurations on the basis of the methods of preparation is self-consistent and appears reasonable, it was thought desirable to have confirmatory evidence. Winstein and Buckles,[15] in their now classical work, have shown that solvolysis of *trans*-1,2-acetoxyhalides in wet acetic acid in the presence of silver acetate proceeds with inversion, the acetoxy group participating. The reaction was applied to 3β,6β-diacetoxy-7α-bromocholestane (XI) and gave the 3β,6β,7β-triol X, identical with the compound obtained by the hydrogenation of the diketone VI. Establishment of the configuration of this *cis*-glycol proves the configuration of the triol obtained by osmium tetroxide hydroxylation: since it must also be a *cis*-glycol, it can only have configuration I.

The configuration of the two *trans*-glycols was confirmed by examining the hydroxyl bands in their infrared spectra by the method of Kuhn[16] (as in the preceding paper). The results are shown in Table I, together with relevant data on the cyclohexanediols. The 6,7-diequatorial triol IX shows a peak corresponding to bonded hydroxyl but the 6,7-diaxial isomer V shows none, as ex-

TABLE I

POSITION OF HYDROXYL BANDS IN THE INFRARED (CM.$^{-1}$)

Compound	Free OH	Bonded OH	Δν
Cholestane-3β,6α,7α-triol (I)	3621	3575	46
Cholestane-3β,6β,7β-triol (X)	3619	3576	43
Cholestane-3β,6α,7β-triol (IX)	3617	3591	26
Cholestane-3β,6β,7α-triol (V)	3629	None	..
cis-Cyclohexane-1,2-diol[a]	3626	3587	39
trans-Cyclohexane-1,2-diol[a]	3634	3602	32

[a] Reference 16.

(4) C. Djerassi and J. Fishman, THIS JOURNAL, **77**, 4291 (1955).
(5) J. Pataki, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 5375 (1951).
(6) C. W. Shoppee, D. N. Jones and G. H. R. Summers, *J. Chem. Soc.*, 3100 (1957).
(7) A. Fürst and Pl. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).
(8) D. R. James, R. W. Rees and C. W. Shoppee, *J. Chem. Soc.*, 1370 (1955).
(9) A. Fürst and Pl. Plattner, Abs. Papers, 12th Intern. Congr. Pure Appl. Chem., New York, 1951, p. 409.
(10) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
(11) G. H. Alt and D. H. R. Barton, *ibid.*, 4284 (1954).
(12) I. M. Heilbron, E. R. H. Jones and F. S. Spring, *ibid.*, 801 (1937).
(13) D. R. James and C. W. Shoppee, *ibid.*, 4224 (1954).
(14) K. Takeda, T. Komeno and K. Igarashi, *Pharm. Bull. (Japan)*, **3**, 352 (1954); *C. A.*, **50**, 12087 (1956).
(15) S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2787 (1942).
(16) L. P. Kuhn, *ibid.*, **74**, 2492 (1952).

pected. The two *cis*-glycols I and X give evidence of stronger hydrogen bonds between the hydroxyl groups. The hydrogen bond in the *cis*-diols is stronger than in *cis*-cyclohexane-1,2-diol, but in the diequatorial *trans* isomer V it is weaker than in *trans*-cyclohexane-1,2-diol; this is explained by a slight deformation of ring B owing to the presence of the axial methyl group.

The cholestanetriols are difficult to obtain crystalline because they have a strong tendency, even in dilute solutions, to form gels; and two of the triols tenaciously retain half a mole of water which is not removed even on heating in high vacuum.

The rates of the reactions of the four triols with lead tetraacetate and with phenyl iodosoacetate are shown in Table II, together with the corresponding data for the cyclohexane-1,2-diols. The most interesting result is that the diaxial isomer is completely resistant to both glycol splitting reagents. The other rates are in the expected order: the diequatorial *trans*-glycol is the slowest and the 6β,7β-derivative the fastest, since in the latter repulsion of the axial hydroxyl group by the angular methyl group at C10 facilitates the closer approach of the hydroxyl groups to each other.

TABLE II

RATES OF REACTION WITH GLYCOL-SPLITTING REAGENTS

Compound	Lead tetraacetate T, °C.	Lead tetraacetate k^a	Phenyl iodosoacetate T, °C.	Phenyl iodosoacetate $100k^a$
Cholestane-3β,6α,7α-triol (I)	25	42	50	12.5
Cholestane-3β,6β,7β-triol (X)	25	160	50	44
Cholestane-3β,6α,7β-triol (IX)	25	2.1	80	30.5
Cholestane-3β,6β,7α-triol (V)	50	No reacn.	80	No reacn.
cis-Cyclohexane-1,2-diol	25	8.11[b]	20	0.08[c]
trans-Cyclohexane-1,2-diol	25	0.316[b]	20	Slow[c]

[a] k is in mole^{-1} l. min.$^{-1}$ in glacial acetic acid. [b] E. L. Eliel and C. Pillar, THIS JOURNAL, **77**, 3600 (1955). [c] R. Criegee and H. Beucker, *Ann.*, **541**, 218 (1939).

Rates for the reaction with periodate were not measured because the insolubility of the triols in water prevented the close control of *p*H and ionic strength. The reactions were carried out in 80% ethanol and their course is shown in Fig. 1. Here, again, the diaxial isomer was not attacked. Surprisingly, however, the rates of the other diastereomers were in an order opposite to that with the other glycol-splitting reagents, the *trans*-glycol reacting considerably faster than the *cis* compounds.

Instances are known in which diaxial glycols were found to split at rates much lower than their diastereomers; for example, *trans*-decalin-2β,3α-diol[17] and 22a,5α-spirostane-3α,4β-diol.[18] In these cases, however, the ring containing the hydroxyl groups is fused only to one other ring and is therefore not as rigid as ring B in the cholestanetriols; the reaction of the diaxial diols is slow but is not prevented.[19]

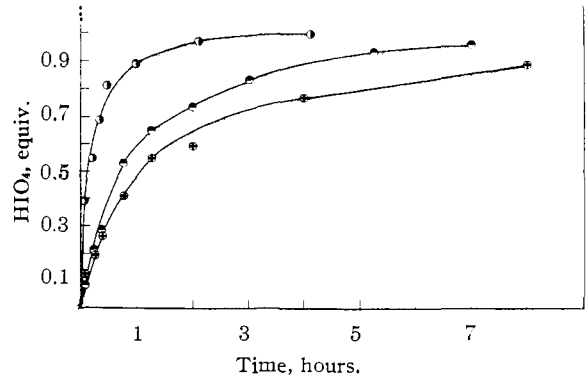


Fig. 1.—Reaction of the cholestanetriols with periodic acid in 80% ethanol at 25°: ◑, cholestane-3β,6α,7β-triol; ◓, -3β,6α,7α-triol; ⊕, -3β,6β,7β-triol.

Existence of a Cyclic Intermediate.—Extensive investigations have shown that in pairs of stereoisomeric glycols faster fission is shown by the isomer in which the hydroxyl groups are nearer—actually or potentially—to each other.[20] In particular, the reaction is extremely fast[21] when the projected valency angle is 0°. It has now been shown that it becomes extremely slow when the projected valency angle is 180°. To explain this strong dependence of the reaction rate on configuration, the existence of cyclic intermediates—or transition states—was postulated.[22]

Other proposed mechanisms[23-25]—not involving cyclic intermediates—have been inspired mainly by the cases of *trans*-decalin-9,10-diol[26] and *trans*-hydrindane-8,9-diol.[27] These glycols react normally with lead tetraacetate although the projected valency angle is 180° and a cyclic intermediate is not possible. There is clear evidence,[28] however, that glycol fission in these cases occurs by a mechanism other than the usual: these two glycols react more slowly in benzene than in glacial acetic acid whereas other glycols react more rapidly. The availability of another mechanism is probably caused by the ditertiary nature of these glycols[29];

(17) Md. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2119 (1958).

(18) C. Djerassi and R. Ehrlich, *J. Org. Chem.*, **19**, 1351 (1954). Another case reported in this paper—that of the 22a,5α-spirostane-2,3-diols—is, however, anomalous, the diaxial glycol being split *faster* than its diequatorial isomer.

(19) Ring B in cholestane derivatives can take up a slightly distorted boat or "skew" conformation [R. E. Reeves, *Ann. Rev. Biochem.*, **27**, 17 (1958)], but apparently the energy of this form is too high to allow a substantial contribution to the reaction.

(20) (a) For lead tetraacetate: R. Criegee, L. Kraft and B. Rank, *Ann.*, **507**, 159 (1933); (b) for phenyl iodosoacetate: R. Criegee and H. Beucker, *Ann.*, **541**, 226 (1939); (c) for periodate: C. C. Price and M. Knell, THIS JOURNAL, **64**, 552 (1942).

(21) R. E. Reeves, *Anal. Chem.*, **21**, 751 (1949).

(22) For lead tetraacetate: R. Criegee, *Sitzungsber. Ges. Naturwiss. Marburg*, **69**, 25 (1934); R. Criegee, *Ann.*, **522**, 75 (1936); *Angew. Chem.*, **50**, 153 (1937); also ref. 20a. For phenyl iodosoacetate: R. Criegee and H. Beucker, *Ann.*, **541**, 226 (1939). For periodate: ref. 20c; F. R. Duke, THIS JOURNAL, **69**, 3054 (1947).

(23) W. A. Waters, "Chemistry of Free Radicals," Oxford Univ. Press, Oxford, Eng., 1946, p. 230.

(24) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford Univ. Press, Oxford, Eng., 1949, p. 276.

(25) J. P. Cordner and K. H. Pausacker, *J. Chem. Soc.*, 102 (1953); K. H. Pausacker, *ibid.*, 107 (1953).

(26) R. Criegee, E. Büchner and W. Walther, *Ber.*, **73**, 571 (1940).

(27) R. Criegee and H. Zogel, *ibid.*, **84**, 215 (1951).

(28) R. Criegee, E. Höger, G. Huber, P. Kruck, F. Marktscheffel and H. Schellenberger, *Ann.*, **599**, 98 (1956).

(29) We are grateful to Dr. G. W. K. Cavill for this suggestion.

the case of cholestane-3β,6β,7α-triol—in which the glycol group has the same geometry—indicates that this alternative mechanism is not avaliable to disecondary glycols. The examples discussed by Waters[30] in an attempt to discredit the cyclic intermediate mechanism are also all ditertiary glycols.

It is surprising—in view of the important role that *trans*-decalin-9,10-diol has played in discussions on the mechanism of glycol fission—that the effect of other glycol-splitting reagents on this diol has not yet been described. We have now filled this gap and have found that *trans*-decalin-9,10-diol reacts normally with phenyl iodosoacetate (k 0.23 mole^{-1} l. min.$^{-1}$ at 50°) but is not attacked by periodate. The iodosoacetates (which closely parallel the behavior of lead tetraacetate but at a slower rate) can therefore utilize an alternate mechanism for ditertiary glycols: but, for periodate, there is no need to postulate any mechanism other than the one involving a cyclic intermediate.[31]

The present and the preceding paper describe two cases in which the variation of the rate of glycol fission within groups of diastereomers is greater than in any other known instance. In this respect the results strongly support the existence of cyclic intermediates in glycol fission.

Experimental[32]

All melting points are corrected. Specific rotations were measured in chloroform, unless otherwise stated, and ultraviolet spectra in 95% ethanol. Light petroleum had b.p. 60–80°. Peter Spence Grade H alumina was used for chromatography and was treated with acid by one of the following methods: (1) It was stirred with hot 2 N nitric acid three times for 30 minutes, washed with hot distilled water until the washings had pH 4, and then three times with hot methanol; it was dried at 270°. (2) Alumina was stirred on the steam-bath for 12 hours with 2 N nitric acid, the acid being changed every hour, then treated as above and dried at 160–180°.

Cholestane-3β,6α,7α-triol (I).—3β-Acetoxycholest-6-ene[8] (1.39 g., m.p. 107.5–108°, [α]D −94°) was added to a solution of osmium tetroxide (1 g.) in anhydrous ether (60 ml.) and anhydrous pyridine (1.5 ml.), and the mixture was allowed to stand in the dark at room temperature for 64.5 hours. The solvent was removed and the residue heated under reflux with sodium sulfite (2.05 g.), water (12 ml.) and ethanol (20 ml.) for 15 minutes. The precipitated osmium was filtered off and the filtrate diluted with water and extracted with chloroform. Removal of the dried solvent left a solid (1.19 g.) which could not be crystallized (gel): it was chromatographed on acid-washed (method 1) alumina (30 g.). Elution with light petroleum and with benzene gave no material, and mixtures of chloroform (10–25%) with benzene gave oils. Chloroform–benzene (1:1) gave **3β-acetoxycholestane-6α,7α-diol (II)** (0.07 g.) which crystallized from ethyl acetate in needles, m.p. 168.5–169.5°, [α]D +30° (c 0.8). *Anal.* Calcd. for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89. Found: C, 75.18; H, 10.81.

Cholestane-3β,6α,7α-triol (0.35 g.) was eluted with chloroform and with 2% ethanol in benzene. Recrystallization from acetone or ethyl acetate gave needles, m.p. 213.5–214.5°, [α]D +39° (c 1 in EtOH). Wintersteiner and Moore[3] reported 211.5–212.5°, [α]D +41°.

The 3-acetate II gave the same triol on hydrolysis with boiling 10% methanolic KOH for 2 hours.

3β-Acetoxycholestane-6β,7α-diol.—A solution of 3β-acetoxy-6α,7α-epoxycholestane[8] (0.12 g., m.p. 177.5–178°, [α]D −34°) in acetone (21 ml.) was mixed with water (2.5 ml.) and 10% sulfuric acid (0.2 ml.) and set aside at room temperature for 76 hours. After neutralization with sodium carbonate, the solution was concentrated under reduced pressure, diluted with water, and extracted with ether. Evaporation of the dried solvent left a solid (0.094 g.); recrystallization from light petroleum or methanol gave 3β-acetoxycholestane-6β,7α-diol as needles, m.p. 189.5–190°, [α]D −15° (c 3).

Anal. Calcd. for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89. Found: C, 75.38; H, 10.62.

Cholestane-3β,6β,7α-triol (V).—3β-Acetoxycholestane-6β,7α-diol (1.35 g.) was refluxed with 10% methanolic potassium hydroxide (60 ml.) for 2 hours. The solution was concentrated, diluted with water and extracted with ether. Evaporation of the dried solvent left a gel which could not be induced to crystallize; it was chromatographed on acid-washed (method 2) alumina (35 g.). Elution with benzene and with chloroform gave negligible quantities of oil. Elution with ethanol gave a solid (1.047 g.), which readily formed a gel and was crystallized with difficulty from methanol to give cholestane-3β,6β,7α-triol as needles, m.p. 193–194°, [α]D +6° (c 1 in EtOH). A sample for analysis was sublimed at 180–220° (0.01 mm.).

Anal. Calcd. for $C_{27}H_{48}O_3$, 0.5 H_2O: C, 75.46; H, 11.49. Found: C, 75.42; H, 11.44.

Alkaline Hydrolysis of 3β-Acetoxy-7α-bromocholestan-6-one (VII). (i) **In Air.**—Potassium hydroxide (10 g.) was added to a boiling solution of the bromoketone[12] (3.75 g.) in methanol (100 ml.) and shaken until dissolved. After a further 2 hours boiling the solution was concentrated, diluted with water and extracted with ether. Evaporation of the dried solvent left a brown gum (3 g.) which crystallized from methanol and then melted at 166–167°, [α]D −22° (c 1). After 3 recrystallizations, it formed needles, m.p. 173.5–174.5°, [α]D −42° (c 1). Heilbron, Jones and Spring[12] reported m.p. 179°, [α]D +31.4° for the product obtained by the alkaline hydrolysis of the bromoketone. A second experiment under the same conditions gave plates, m.p. 171–172°, [α]D −22° (c 1), after two recrystallizations from methanol.

The crude product (5.7 g., [α]D −17°) obtained from another alkaline hydrolysis of the bromoketone was chromatographed on acid-washed (method 1) alumina (130 g.). The first two fractions (chloroform–benzene, 1:3) and the third fraction (chloroform–benzene, 1:1) had rotations of about +30° and gave crystalline products from methanol: (1) 0.7 g., leaflets, m.p. 180–181°, [α]D +48° (c 0.7), λ_{max} 276–278 mμ (log ϵ 2.58); (2) 0.5 g., plates, m.p. 176–177°, [α]D +30° (c 0.6), λ_{max} 275 mμ (log ϵ 2.22); (3) 0.3 g., lathes, m.p. 178–180°, [α]D +27° (c 1), λ_{max} 277 mμ (log ϵ 1.99). These products did not depress each other's melting points and gave correct analyses for a dihydroxycholestanone.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.47; H, 11.08. Found: (1) C, 77.03; H, 11.09; (2) C, 77.51; H, 10.77; (3) C, 77.35; H, 10.95.

The dibenzoate, prepared from material (0.05 g.) obtained from fraction 1 with benzoyl chloride (0.5 ml.) in pyridine (1 ml.), crystallized from methanol in needles, m.p. 174.5–175°, [α]D +68° (c 1). Heilbron, *et al.*,[12] reported m.p. 169–170°, [α]D +62° for the dibenzoate of the product obtained from the alkaline hydrolysis of the bromoketone.

Anal. Calcd. for $C_{41}H_{54}O_5$: C, 78.55; H, 8.65. Found: C, 78.65; H, 8.65.

Fraction 5, eluted with chloroform, crystallized from methanol in laths (0.22 g.), m.p. 164–166°, [α]D −10° (c 1). Analysis showed C, 75.61; H, 10.20. Benzoylation gave compound, m.p. 213–214°, [α]D +59° (c 1), containing C, 77.49; H, 8.64. Fraction 6, eluted with methanol, crystallized from methanol as plates (0.15 g.), m.p. 209–211°, [α]D +34° (c 0.5). Analysis showed C, 78.65; H, 11.49. This material had no absorption in the carbonyl region of the infrared spectrum.

Fraction 7, eluted with acetic acid–methanol (1:9), gave an olive-green color with ferric chloride and a yellow color with tetranitromethane. It crystallized from methanol in plates, m.p. 151–152°, [α]D −99° (c 1), λ_{max} 277 mμ (log ϵ 3.97), and did not depress the melting point of 3β-hydroxycholestane-6,7-dione.[33]

(30) P. Levesley, W. A. Waters and A. N. Wright, *J. Chem. Soc.*, 840 (1956).

(31) G. J. Buist and C. A. Bunton, *J. Chem. Soc.*, 1406 (1954).

(32) The microanalyses were performed by Dr. E. Challen and Mr. D. Weeden. The infrared spectra were taken by Mr. I. Reece.

(33) C. W. Shoppee, *J. Chem. Soc.*, 1032 (1948).

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.66; H, 10.60.

To further identify this material as 3β-hydroxycholestane-6,7-dione, two derivatives were prepared; 45 mg. was fused with *o*-phenylenediamine (45 mg.) for 40 minutes at 140–150°. The resultant dark mass was heated on the steam-bath for 1 hour with acetic anhydride (1 ml.) and pyridine (2 ml.). Water was added, the mixture extracted with chloroform, the solvent evaporated and the residue crystallized from methanol to give the quinoxaline derivative (13 mg.), m.p. 189–191°, undepressed on admixture with a sample made from 3β-acetoxycholestane-6,7-dione. Heilbron, *et al.*,[12] reported m.p. 186–187°.

In a mixture of benzoyl chloride (0.5 ml.) and anhydrous pyridine (1.5 ml.) 56 mg. of the substance was dissolved. After 2 days at room temperature ice was added and the precipitate crystallized from methanol to give the enolic dibenzoate (61 mg.), m.p. 177°, $[\alpha]_D$ −28° (*c* 0.8). Benzoylation of 3β-hydroxycholestane-6,7-dione[33] gave material identical in all respects, including its infrared spectrum.

Anal. Calcd. for $C_{41}H_{52}O_5$: C, 78.81; H, 8.39. Found: C, 78.31; H, 8.34.

(ii) **Under Nitrogen.**—3β-Acetoxycholestan-6-one (8.0 g.) was refluxed with a solution of potassium hydroxide (24 g.) in methanol (240 ml.) under an atmosphere of oxygen-free nitrogen. The bromoketone slowly dissolved; after 2 hours the red solution was diluted with water and extracted with ether. Evaporation of the dried solvent left a gum (6 g.) which was recrystallized twice from methanol to give needles (4.7 g.), m.p. 171–174°, $[\alpha]_D$ +25° (*c* 0.9).

Cholestane-3β,6α,7β-triol (IX).—The product (4.7 g., $[\alpha]_D$ +25°) obtained from the alkaline hydrolysis of the bromo-ketone under nitrogen was dissolved in freshly distilled 1-butanol (70 ml.). Sodium in small pieces was added to the boiling solution until no more dissolved. Excess sodium was decomposed by addition of ethanol, water was added and the butanol removed by steam distillation. The residue was extracted with ether; evaporation of the dried solvent left a brown resin, $[\alpha]_D$ +43° (*c* 0.9 in EtOH). The resin was chromatographed on acid-washed (method 2) alumina (140 g.) prepared in benzene. The last fraction, eluted with ethanol–benzene (4:6), contained a solid (1.7 g.), $[\alpha]_D$ +50°, which readily formed gels in organic solvents, and was difficult to obtain crystalline; careful crystallization from acetone gave cholestane-3β,6α,7β-triol as plates, m.p. 230.5–231.5°, $[\alpha]_D$ +60° (*c* 1 in EtOH).

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 77.09; H, 11.50. Found: C, 76.89; H, 11.43.

Tosylation gave a **ditosyl derivative**: the triol (0.19 g.) and tosyl chloride (0.4 g.), dissolved in pyridine (2 ml.), were allowed to stand for 3 weeks. Addition of ice gave a gum (0.22 g.) which crystallized from methanol in needles, m.p. 165–166°, $[\alpha]_D$ +9° (*c* 1).

Anal. Calcd. for $C_{41}H_{60}O_7S_2$: C, 67.54; H, 8.29. Found: C, 67.67; H, 8.17.

Cholestane-3β,6β,7β-triol (X).—(i) 3β-Acetoxycholestane-6,7-dione was prepared according to Heilbron, *et al.*[12] but the yield was increased to 64% by shortening the time of heating to 2 hours. A mixture of the diketone (3.99 g.), acetic acid (375 ml.), hydrochloric acid (2 drops) and platinum oxide (1 g.) was shaken in an atmosphere of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off, the solvent removed under reduced pressure and the residue dissolved in ether and washed with sodium hydrogen carbonate and water. Evaporation of the dried solvent left a yellow treacle (3.97 g.), $[\alpha]_D$ +26° (*c* 1 in EtOH), which crystallized at −40°, but melted at room temperature. It was heated under reflux with 10% methanolic potassium hydroxide (100 ml.) for 2 hours. The mixture was concentrated, diluted with water and extracted with ether. Evaporation of the dried solvent left a pale yellow solid (2.85 g.); careful recrystallization from acetone gave cholestane-3β,6β,7β-triol, $[\alpha]_D$ +51° (*c* 1.5 in EtOH). It melts at 168°, resolidifies, and melts again at 173°.

Anal. Calcd. for $C_{27}H_{48}O_3 \cdot 0.5H_2O$: C, 75.46; H, 11.49; O, 13.05. Found: C, 75.90; H, 11.32; O, 12.8. After repeated sublimations at 210–220° (0.05 mm.): Found: C, 75.28, 75.24; H, 11.45, 11.44; O, 12.6.

The **triacetate**, made by acetylation with acetic anhydride–pyridine(1:2) at room temperature for one week, crystallized from methanol in prisms, m.p. 94.5–95.5°, $[\alpha]_D$ +24° (*c* 0.7).

Anal. Calcd. for $C_{33}H_{54}O_6$: C, 72.49; H, 9.96; acetyl, 23.61. Found: C, 72.46; H, 9.67; acetyl, 21.6.

(ii) A mixture of 3β-hydroxycholestane-6,7-dione[33] (0.22 g.), acetic acid (25 ml.), hydrochloric acid (1 drop) and platinum oxide (0.05 g.) were shaken in an atmosphere of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the solvent removed under reduced pressure. The residue formed gels with most solvents, but crystallized readily from acetic acid–light petroleum to give cholestane-3β,6β,7β-triol as fine needles, m.p. 164° and 171.5–172.5°, $[\alpha]_D$ +49° (*c* 0.5 in EtOH).

Anal. Calcd. for $C_{27}H_{48}O_3 \cdot 0.5CH_3CO_2H$: C, 74.62; H, 11.18. Found: C, 74.53, 74.93; H, 11.18, 11.30. After sublimation at 220° (0.1 mm.): Calcd. for $C_{27}H_{48}O_3$: C, 77.09; H, 11.50. Found: C, 76.82; H, 11.59.

After washing with water and recrystallization from acetone the hemihydrate, m.p. 164° and 173.5°, was obtained.

Anal. Calcd. for $C_{27}H_{48}O_3 \cdot {}^1/_2H_2O$: C, 75.46; H, 11.49. Found: C, 75.47; H, 11.51. After sublimation at 180° (0.01 mm.): Found: C, 75.29; H, 11.36.

3β,6β-Diacetoxy-7α-bromocholestane (XI).—3β-Acetoxy-7α-bromocholestan-6-one was reduced with sodium borohydride. The chromatographic separation of the epimers, described by James and Shoppee,[13] could not be repeated: separation was poor and even on acid-washed (method 2) alumina some of the diaxial isomer was converted to 3β-acetoxycholestane-6β,7α-diol. However, fractional crystallization of the reduction mixture from light petroleum gave 3β-acetoxy-7α-bromocholestan-6β-ol, m.p. 177–179°, $[\alpha]_D$ −26° (*c* 1).

A mixture of the bromohydrin (0.25 g.), anhydrous pyridine (2 ml.) and acetic anhydride (1 ml.) was set aside at room temperature for 20 hours. Addition of ice gave a gum (0.2 g.) which was chromatographed on acid-washed (method 2) alumina (18 g.); elution with light petroleum–benzene mixtures gave 3β,6β-diacetoxy-7α-bromocholestane (0.12 g.), needles from methanol, m.p. 132–133°, $[\alpha]_D$ −12° (*c* 1.2).

Anal. Calcd. for $C_{31}H_{51}O_4Br$: C, 65.58; H, 9.06. Found: C, 65.26; H, 8.79.

Reaction of 3β,6β-Diacetoxy-7α-bromocholestane with Silver Acetate in Moist Acetic Acid.—A mixture of the bromo compound (86 mg.), freshly prepared silver acetate (32 mg.), acetic acid (4 ml.) and water (1 drop) was heated, with stirring, for 6 hours at 100–110°. The mixture was filtered, the filtrate evaporated to dryness under reduced pressure and the residue refluxed with 10% methanolic potassium hydroxide (10 ml.) for 2 hours. The solution was concentrated, diluted with water and extracted with chloroform. The chloroform extract was washed with water, saturated sodium chloride solution and water. Evaporation of the dried solvent and recrystallization from acetic acid–light petroleum gave cholestane-3β,6β,7β-triol (48 mg.), m.p. and mixed m.p. 164 and 172°, $[\alpha]_D$ +52° (*c* 0.2 in EtOH).

Kinetic Runs.—The reaction rates were determined as described in the preceding paper[2]; the "Dreischenkelrohr" tube was used in the runs with lead tetraacetate and the 3β,-6β,7β-triol and the 3β,6α,7α-triol. The triols were dissolved in glacial acetic acid before addition of the oxidizing agent. The concentration of the glycols was approx. 0.001 *M*, except for *trans*-decalin-9,10-diol[34] (0.003 *M*) and for the fast runs in the "Dreischenkelrohr" (0.0005 *M*); the concentration of the oxidizing agent was approx. 0.01 *M*. After 8 hours, cholestane-3β,6β,7α-triol had consumed no lead tetraacetate at 50° or phenyl iodosoacetate at 80°.

For the reaction with periodate, the cholestanetriols (0.0225 g.) and *trans*-decalin-9,10-diol (0.0100 g.) were dissolved in ethanol and 10 ml. of a 0.001 *M* solution of paraperiodic acid in water was added, followed by ethanol to bring the volume to 50 ml. At intervals, 5-ml. aliquots were removed and run into 10 ml. of 0.1 *N* hydrochloric acid containing a few crystals of potassium iodide. The liberated iodine was titrated with 0.014 *N* thiosulfate solution. The results are shown in Fig. 1. Titrations in the runs with the 3β,6β,7α-triol and with decalindiol at 40° were the same as those of a blank.

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(34) S. Dev, *J. Indian Chem. Soc.*, **31**, 1 (1954).