TABLE V

Investigators	Temp., °C.	$2k_3$ (10^{-7})	k_2 (10^{-3})	k_4
Burnett and Melville[5]	15.9	280 (av.)	0.72 (av.)	None
Swain and Bartlett[7]	25	4	.55	...
Dixon-Lewis[17]	0	20	1.8	0.123
Matheson, *et al.*[8]	25	5.88	1.012	5 (at 50°)
This paper	25	5.9	1.0	0.25[a]
				0.23[b]

[a] On the basis of union of radicals. [b] On the basis of disproportionation of radicals.

one to expect. The value of the chain transfer constant is not in good agreement with that from the other laboratories. The equations used by us neglect chain transfer to the initiator, a reaction which would have been important if benzoyl peroxide were being used but which does not seem to require consideration with either di-*t*-butyl peroxide[18] used by us or α-azo-bis-isobutyronitrile used by Matheson, *et al.*[19]

Summary

A much improved apparatus is described for determining absolute rate constants of liquid bulk polymerization by means of the rotating sector. Errors from previously recognized sources have been greatly curtailed. The results of a redetermination of the absolute rate constants for the steps in the polymerization of liquid vinyl acetate are reported and are compared in Table V with the results of other investigators.

(18) J. H. Raley, F. F. Rust and W. E. Vaughan, THIS JOURNAL, **70**, 88 (1948).

(19) F. M. Lewis and M. S. Matheson, *ibid.*, **71**, 747 (1949).

CAMBRIDGE, MASS. RECEIVED AUGUST 5, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IMPERIAL COLLEGE, LONDON]

Stereochemistry of the Cholesterol Dibromides[1]

BY D. H. R. BARTON[2] AND E. MILLER

The previous paper[3] in this series dealt with the elucidation of the stereochemistry of the two cholesterol dichlorides. Ordinary cholesterol dichloride, obtained by the addition of chlorine to cholesterol, was shown to be 5α,6β-dichlorocholestan-3β-ol, whilst the isomeric dichloride, obtained by the use of the iodobenzene dichloride reagent, was demonstrated to be 5α,6α-dichlorocholestan-3β-ol. In logical extension of this work the stereochemistry of the two cholesterol dibromides has now been investigated.

In the course of their extensive bromination studies Butenandt and Schramm[4] noted that dibromocholestanone, obtained by oxidation[4,5] of ordinary cholesterol dibromide, was monobrominated exclusively at the 4-position. Since cholestanone and coprostanone are brominated,[6] under comparable conditions, at the 2- and 4-positions, respectively, Butenandt and Schramm concluded that ordinary cholesterol dibromide probably had the coprostane configuration of rings A and B.

In actual fact this argument appears to be unsound because it is not based on a proper appreciation of the mechanism[7] of the bromination of ketones, the rate controlling step of which is the abstraction of a proton from the ketone by a base. Other factors being equal, the most acidic available proton will be removed. In the case under consideration here the powerful negative (acid strength increasing) inductive effect of the 5-bromine atom will clearly be dominant and thus lead to substitution at the 4-position irrespective of the nature of the A/B ring fusion.

The mechanism of the ionic type addition of bromine to olefinic linkages is generally accepted as comparable to that of chlorine, particularly in its stereochemical (*trans*-addition) implications.[8] It might be expected therefore, by analogy with the established[3] configuration of the dichloride, that ordinary cholesterol dibromide would be 5α,6β-dibromocholestan-3β-ol. This assignment of configuration is also suggested by the molecular rotation data summarized in Table I. Not only has ordinary cholesterol dibromide almost identical Δ values with those recorded[3] for 5α,6β-dichlorocholestan-3β-ol, but the absolute magnitudes of the optical rotations are similar. The 5α,-6β-configuration was finally confirmed chemically by treating the known cholesterol α-oxide with

TABLE I

Substance	$[M]_D$[a] Alcohol	Acetate	Benzoate	Ketone	Δ_1[b]	Δ_2	Δ_3
5α,6β-Dichlorocholestan-3β-ol[c]	−123	−145	−112	−123	−22	+9	±0
5α,6β-Dibromocholestan-3β-ol	−240	−271	−234	−245	−31	+6	−5

[a] All rotations in chloroform solution. [b] Δ_1 is the molecular rotation difference on acetylation, Δ_2 that on benzoylation and Δ_3 that on oxidation. [c] Data from Barton and Miller.[3]

(1) This paper is Part XV in our series on the "Application of the Method of Molecular Rotation Differences to Steroids." It was supported, in part, by a research grant from the Chemical Society, London.

(2) Harvard University, Visiting Lecturer, 1949–1950.

(3) Barton and Miller, THIS JOURNAL, **72**, 370 (1950).

(4) Butenandt and Schramm, *Ber.*, **69**, 2289 (1936).

(5) Inhoffen, *ibid.*, **69**, 1134, 2141 (1936).

(6) Butenandt and Wo ff, *ibid.*, **68**, 2091 (1935); compare Butenandt and Mamoli, *ibid.* **8**, 1854 (1935); Djerassi and Scholz, *Experientia*, **3**, 107 (1947).

(7) *E. g.*, see Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., p. 96 ff.

(8) Michael, *J. prakt. Chem.*, **52**, 344 (1893); McKenzie, *J. Chem. Soc.*, **101**, 1196 (1912); Terry and Eichelberger, THIS JOURNAL, **47**, 1067 (1925); Roberts and Kimball, *ibid.*, **59**, 947 (1937).

hydrobromic acid to give 5α-hydroxy-6β-bromocholestan-3β-ol, which was oxidized to the corresponding 3-ketone. Dehydration of the latter afforded 6β-bromo-Δ⁴-cholesten-3-one, which was identical with the 6-bromo-Δ⁴-cholesten-3-one obtained earlier[9] by dehydrobromination of the 3-ketone prepared by oxidation of ordinary cholesterol dibromide.

Many years ago Mauthner[10,11] discovered that ordinary cholestene dibromide underwent mutarotation when left in solution at room temperature, and finally gave a strongly dextrorotatory isomeric dibromide. After earlier work,[12] which led to some confusion in the literature, Bretschneider[13] and his colleagues showed that ordinary cholesterol benzoate dibromide exhibited similar mutarotation to give an equilibrium mixture, from which a new "stable" cholesterol benzoate dibromide was readily isolated. We have confirmed this work. Furthermore we found that when ordinary cholesterol dibromide was left in chloroform solution at room temperature for a few days, a new "stable" dibromide was formed, the relationship of which to the "stable" benzoate dibromide mentioned above was confirmed by benzoylation. All these stable dibromides are characterized by their remarkable crystallinity, as well as by high positive rotations.

The configuration of the new cholesterol dibromide was established in the following way. Chromic acid oxidation afforded the corresponding 3-ketone, which was dehydrobrominated to a 6-bromo-Δ⁴-cholesten-3-one, not identical with the 6β-bromo-compound mentioned above. Its formulation as 6α-bromo-Δ⁴-cholesten-3-one is confirmed by the absorption spectrum and by the high positive rotation, there being a similar difference in molecular rotation (Table II) between the two 6-bromo-Δ⁴-cholesten-3-ones as between the two analogous 6-chloro-compounds.[3]

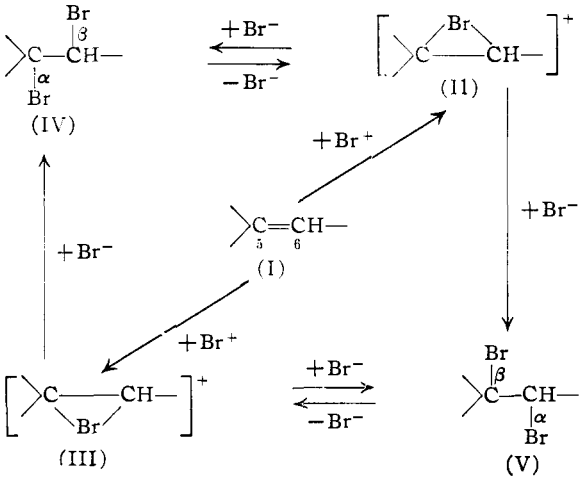
TABLE II

Ketone	$[M]_D$[a] 6β-	6α-	$([M]_D$ 6α-) − $([M]_D$ 6β-)
6-Chloro-Δ⁴-cholesten-3-one[b]	+65	+247	+182
6-Bromo-Δ⁴-cholesten-3-one	+28	+245	+217

[a] All rotations in chloroform solution. [b] Data from Barton and Miller.[3]

This chemical evidence proves that the "stable" cholesterol dibromide must be either 5α,6α- or 5β,6α-. Now, in contrast to 5α,6β-dichlorocholestan-3β-yl benzoate, 5α,6α-dichlorocholestan-3β-yl benzoate undergoes a facile elimination of hydrogen chloride when treated with alkali,[3,14] a reaction to be expected of a *cis*-1,2-dihalide.[15] The new "stable" cholesterol benzoate dibromide behaves quite differently. It is attacked by alkali even more slowly (see Experimental) than the ordinary (5α,6β-) benzoate dibromide. Similarly "stable" cholestene dibromide does *not* lose hydrogen bromide easily when treated with alkali. This lack of reactivity must mean that the "stable" dibromides have the (*trans*-) 5β,6α-configuration.

It is not inappropriate at this stage to give some explanation of the mechanism of interconversion of the two series of Δ⁵-dibromides. A full appreciation of this mechanism, which is outlined in the scheme below, requires also consideration of the method of formation of the ordinary dibromide.[16] In principle the addition of bromine to cholesterol (I) can be formulated as proceeding through the bromonium ions (II) and (III) to give, respectively, the ordinary dibromide (IV) and the "stable" dibromide (V).[17] Loss of a bromanion from (IV) would give back (II) and the corresponding loss from (V) would give back (III).



Now the ionic addition of unsymmetrical addenda to unsymmetrical olefins proceeds in accordance with Markownikoff's rule. The implication of this is that, since olefins are nucleophilic in reactivity, the second stage of addition involves the "negative" portion of the addendum attaching

(9) Ruzicka, *et al.*, *Helv. Chim. Acta*, **19**, 1147 (1936); Dane, Wang and Schulte, *Z. physiol. Chem.*, **245**, 80 (1937).

(10) Mauthner and Suida, *Monatsh.*, **15**, 91 (1894).

(11) Mauthner, *ibid.*, **27**, 421 (1906).

(12) Dorée and Orange, *J. Chem. Soc.*, **109**, 53 (1916); Petrow, *ibid.*, 1077 (1937).

(13) Bretschneider, *et al.*, *Ber.*, **74**, 1451 (1941).

(14) Berg and Wallis, *J. Biol. Chem.*, **162**, 683 (1946).

(15) Hückel, Tappe and Legutke, *Ann.*, **543**, 191 (1940); Cristol, THIS JOURNAL, **69**, 338 (1947); compare Hughes, Ingold, *et al.*, *J. Chem. Soc.*, 2093 (1948).

(16) The remarks made here with regard to the addition of bromine to cholesterol apply equally well to chlorine. To save space the subject was not discussed previously.[3] In view of the uncertainty (de la Mare, *Quart. Rev.*, **3**, 126 (1949)) with regard to the finer details of halogen addition the treatment is necessarily somewhat formal. It should also be noted that if the C₅ bromine atom could ionize off in the first stage of the rearrangement, then the difficulties mentioned in the text no longer apply. However it seems extremely unlikely that the removal of a secondary bromine (C₆) should take place in preference to a tertiary bromine (C₅), and therefore the possibility has not been discussed in detail.

(17) Since (IV) is almost the sole initial product of the reaction, the two cholesterol dibromides provide a first-class example of kinetic as opposed to thermodynamic control of reaction products; compare de la Mare, Hughes and Ingold, *J. Chem. Soc.*, 17 (1948).

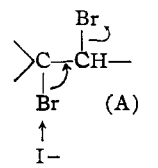
itself to the more heavily substituted carbon atom. The observation of the "negative" portion attacking the less heavily substituted carbon atom is not usually possible. We suggest, however, that the rearrangements of (IV) to (V) through (II) and of (V) to (IV) through (III), constitute a special case. Although the great majority of bromanions which attack the bromonium ions (II) and (III) behave normally, yet a small proportion may be regarded as reacting abnormally and furnishing (V) and (IV), respectively. For most ionic olefin addition reactions such abnormal processes cannot be observed, even if the free energy relationships be favorable, because of irreversibility. The case under discussion is, therefore, a special stereochemical demonstration of *ionic* "non-Markownikoff" addition.

There is an alternative mechanism for the rearrangement, which has been excluded by experiment. If the bromonium ions (II) and (III), formed in the rearrangement, can revert to the original olefin, then the theoretical difficulties mentioned above are avoided. However, this second mechanism seems unlikely because the mutarotation proceeded at the same rate, and to give the same products, both in the presence and the absence of a thirty-fold molar excess of cyclohexene. It seems hardly possible, therefore, that molecular bromine or bromine cations are ever set free during the reaction or cyclohexene dibromide and Δ^5-cholestene would have resulted.

The dextrorotatory cholesterol benzoate dibromide described above has been referred to as the "stable" isomer, because the equilibrium mixture[13] contains about 4 parts of this compound to 1 part of the ordinary dibromide, no matter whether the solvent be chloroform, benzene or acetone. The same applies to cholestene dibromide in chloroform solution.[11] Equating the free energy difference between the two isomers to $RT \log_e K_c$ indicates that the $5\beta,6\alpha$-dibromides are about 800 cal. more stable than the ordinary $5\alpha,6\beta$-dibromides. On the basis of interaction between non-bonded atoms,[18,19] this suggests that the hindrance between a 6β-substituent and the C_{10} methyl group is of greater significance than the comparable increase in repulsive non-bonded interaction energy involved in going from *trans*-decalin to the *cis*-isomer.[19]

The investigations of Young, *et al.*,[20] established that the debromination of *trans*-1,2-dibromides by potassium iodide should proceed more rapidly than that of the isomeric *cis*-dibromides. It appeared of interest, therefore, to examine the applicability of this generalization to the two different types of *trans*-1,2-dibromides of the cholestane series. Ordinary cholesterol benzoate dibromide was rapidly debrominated by potassium iodide, but the isomeric $5\beta,6\alpha$-dibromide scarcely reacted with this reagent. This extraordinary difference in reactivity finds explanation in a stereochemical principle which is undoubtedly of considerable importance in elimination reactions.

The elimination of bromine under the influence of iodide ions is regarded[20] as involving a four-center type transition state as illustrated in (A). For a minimization of the activation energy quantum-mechanical theory[21] indicates that the four centers must lie in one plane. When rotation about the C–C bond is possible, as for example in 1,2-dibromethane,[22] the two halogen atoms are easily able to take up the necessary conformation[23] for activation energy minimization. The same applies for simple cyclohexane derivatives, as already emphasized by Hughes, Ingold, *et al.*,[24] for here the necessary coplanarity is achieved by two *trans*-substituents when both are polar.[25] *cis*-Substituents are unable to take up this conformation on geometrical grounds.



(A)

The application to the particular case under discussion may be more easily demonstrated by reference to model drawings. Figure 1 shows ordinary cholesterol dibromide, derived from *trans*-decalin. Immediately alongside is depicted in (B) the view obtained on looking along the $C_5:C_6$ axis from C_5 to C_6. Clearly C_5,C_6 and the two bromine atoms lie in one plane, as required for the observed facile elimination. Figure 2 shows in a similar fashion $5\alpha,6\alpha$-dichlorocholestan-3β-ol and (C) the corresponding view on looking along the $C_5:C_6$ axis. Since C_5(Cl) and C_6(H) are in one plane with C_5 and C_6 the very easy elimination[3,14] of hydrogen chloride is understandable. As a corollary the stability of the $5\alpha,6\beta$-compounds[3] to alkali is readily comprehensible. If *cis*-decalin be taken to have the two-chair form for which evidence has recently been advanced,[19,26] then the "stable" cholesterol dibromide may be illustrated as in Fig. 3. (D) represents the view looking down the $C_5:C_6$ axis, and shows that C_5,C_6 and the two bromine atoms are *not* in one plane. The

(18) Dostrovsky, Hughes and Ingold, *J. Chem. Soc.*, 173 (1946); Westheimer and Mayer, *J. Chem. Phys.*, **14**, 733 (1946); Hill, *ibid.*, **14**, 465 (1946); **16**, 399, 938 (1948).

(19) Barton, *J. Chem. Soc.*, 340 (1948).

(20) Young, Pressman and Coryell, THIS JOURNAL, **61**, 1640 (1939); Winstein, Pressman and Young, *ibid.*, **61**, 1645 (1939).

(21) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 90; compare Hughes, Ingold, *et al.*, *J. Chem. Soc.*, 2117 (1948).

(22) *Inter al.*, Wu, *J. Chem. Phys.*, **7**, 965 (1939); Beach and Turkevich, THIS JOURNAL, **61**, 303 (1939); Kohlrausch and Wittek, *Z. physik. Chem.*, **B47**, 55 (1940).

(23) This is a convenient term common in sugar chemistry.

(24) Hughes, Ingold, *et al.*, *J. Chem. Soc.*, 2117 (1948).

(25) Beckett, Pitzer and Spitzer, THIS JOURNAL, **69**, 2488 (1947); polar corresponds to ϵ on Hassel's nomenclature (see Hassel and Ottar, *Acta Chem. Scand.*, **1**, 929 (1947)).

(26) Bastiansen and Hassel, *Nature*, **157**, 765 (1946); Hassel and Viervoll, *Acta Chem. Scand.*, **1**, 149 (1947), and papers there cited.

difficulty of elimination is thus explained. However, if *cis*-decalin be assumed to have the classical Sachse–Mohr two-boat conformation, then the "stable" dibromide must be represented as in Fig. 4, with (E) showing the view down the $C_5:C_6$ axis. Here C_5,C_6 and the bromine atoms do lie in one plane, and thus the difficulty of elimination is not made intelligible. In so far as our stereochemical arguments are valid, they provide additional support for the existence of the two-chair *cis*-decalin.

The solution of the problem of the stereochemistry of ordinary cholesterol dibromide implies that the configurations of the other 5,6-dibromides described in the steroid series are also 5α,6β-. It is also likely that the "labile" Δ⁴-cholestene dibromide of Mauthner[27] has the 4β,5α-configuration, and that the "stable" isomer has the 4α,5β-configuration.[28] The two 4,5,6-tribromocholestan-3-ones m. p.'s 106° and 138°, recorded in the literature,[4,5] must be 4β,5α,6β- and 4α,5α,6β-, respectively.

The two stereoisomeric 6-bromo-Δ⁴-cholesten-3-ones mentioned above behave in the same[3] way as their 6-chloro-analogs toward the 2,4-dinitrophenylhydrazine reagent. In the cold the orange compound, m. p. 245°, the nature of which was discussed previously,[3] is formed from both isomers.

Experimental[29]

5α,6β-Dibromocholestan-3β-ol.—Ordinary cholesterol dibromide, its acetate and benzoate, were prepared according to the directions of Windaus.[30] Recrystallized[31] from ethyl acetate–methanol cholesterol dibromide had m. p. 112–114° decomp., $[\alpha]_D$ −44° (*c*, 5.69), $[M]_D$ −240°. Treated similarly the acetate had m. p. 112–114° decomp., $[\alpha]_D$ −46° (*c*, 3.32), $[M]_D$ −271°, and the benzoate m. p. 135–136° decomp., $[\alpha]_D$ −33° (*c*, 2.03). 5α,6β-Dibromocholestan-3-one was prepared by chromic acid oxidation of cholesterol dibromide.[5] Recrystallized from chloroform–methanol it had m. p.[32] 72–74° decomp., $[\alpha]_D$ −53° (*c*, 4.51), $[M]_D$ −245°. After standing for twenty hours in chloroform solution at room temperature the specific rotations of the four dibromides mentioned above were, respectively, −29, −43, −28° and too dark to read. ●

An analysis on the benzoate 5α,6β-dibromide confirmed the results of Bretschneider, *et al.*[18]

Anal. Calcd. for $C_{34}H_{50}Br_2O_2$: Br, 24.57. Found: Br, 24.7.

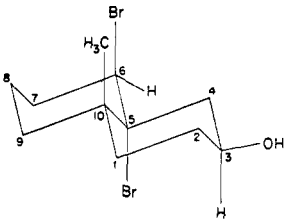
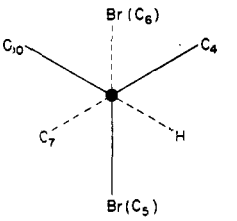


Fig. 1



(B)

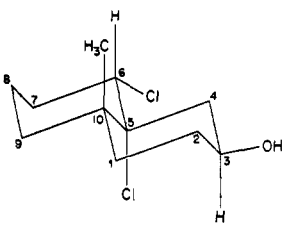
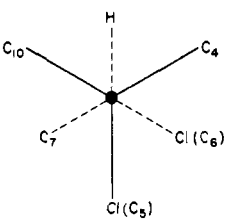


Fig. 2.



(C)

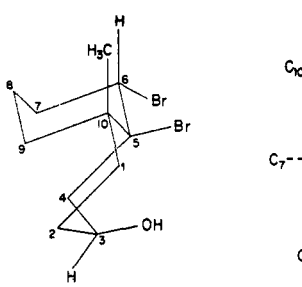
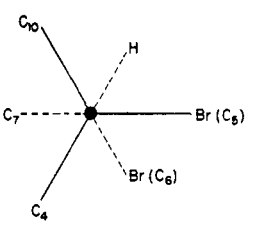


Fig. 3.



(D)

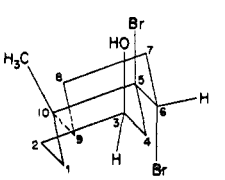
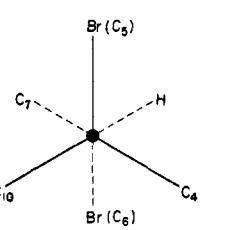


Fig. 4.



(E)

Mutarotation of 5α,6β-Dibromocholestane.—5α,6β-Dibromocholestane, prepared from Δ⁵-cholestene by the method of Windaus[30] and recrystallized from chloroform–ethyl acetate, had m. p. 109–110° decomp., $[\alpha]_D$ −39° (*c*, 2.77), $[M]_D$ −207°. After standing for twenty hours in chloroform solution at room temperature $[\alpha]_D$ was −2°. After standing for three days 5β,6α-dibromocholestane recrystallized from ethyl acetate–methanol, m. p. 143–144° dec., $[\alpha]_D$ + 52° (*c*, 1.81), was readily isolated. 5β,6α-Dibromocholestane furnished Δ⁵-cholestene (identity confirmed by mixed m. p.) on debromination with zinc dust in acetic acid in the usual way. Attempts to dehydrobrominate 5β,6α-dibromocholestane by treatment with various alkaline reagents led either to the recovery of starting material unchanged or to uncrystallizable gums.

The mutarotation of 5α,6β-dibromocholestane was also studied in the presence of cyclohexene and of cyclohexane. The results are summarized in the table below.

(27) Mauthner, *Monatsh.*, **17**, 29 (1896); **28**, 1113 (1907).

(28) A further point of stereochemistry upon which it is difficult to obtain direct information is the configuration at the 5-position in cholesterol hydrochloride. It seems fairly certain from the molecular rotation data as well as from general arguments that this and analogous compounds have the 5α-configuration for the halogen atom.

(29) M. p.'s are not corrected. All specimens were dried *in vacuo* at 20° below their m. p.'s, or at 120°, whichever was the lower temperature, before taking the rotation. All rotations are for the sodium D line and in chloroform solution. The measurements were made at room temperature which varied from 20 to 30°. All values of $[\alpha]_D$ have been approximated to the nearest degree. Concentrations (*c*) are expressed in g. per 100 ml. of solution.

Micro-analyses are by Drs. Weiler and Strauss, Oxford.

(30) Windaus, *Ber.*, **39**, 518 (1906).

(31) All 5α,6β-dibromo-compounds were recrystallized below 30°.

(32) Inhoffen[4] gave m. p. 68–69°, but Butenandt and Schmidt-Thomé (*Ber.*, **69**, 882 (1936)) found m. p. 80°.

Concn. of 5α, 6β-dibromocholestane, wt./vol. %	Solvent	Molar ratio of hydrocarbon to dibromide	[α]D 0 hrs.	[α]D 18 hrs.	[α]D 7 days	Yield,[a] %
2.43	1 Cyclohexane: 9CHCl3	1:20	−36	−12	+34	70
1.91	1 Cyclohexene: 9CHCl3	1:27	−38	−10	+39	63

[a] Of 5β,6α-dibromocholestane, m. p. 143–144° decomp.

6β-Bromo-Δ⁴-cholesten-3-one.—Cholesterol α-oxide[8] (200 mg.), dissolved in 25 ml. of chloroform, was shaken with 25 ml. of 48% aqueous hydrobromic acid for fifteen minutes. After removal of the chloroform *in vacuo* and recrystallization from ethyl acetate–petroleum ether (b. p. 40–60°) in the cold, 5α-hydroxy-6β-bromocholestan-3β-ol was obtained in almost quantitative yield, m. p. 134–135° dec.

Anal. Calcd. for $C_{27}H_{47}BrO_2$: Br, 16.5. Found: Br, 17.1.

Oxidation of this alcohol by chromic acid as described previously[3] for the corresponding chloro-compound gave 5α-hydroxy-6β-bromocholestan-3-one, recrystallized in the *cold* from chloroform–petroleum ether (b. p. 40–60°), m. p. 182° decomp.

Anal. Calcd. for $C_{27}H_{45}BrO_2$: Br, 16.6. Found: Br, 17.8.

This hydroxy-ketone was dehydrated by thionyl chloride–pyridine, exactly as described previously[3] for the corresponding chloro-compound, to furnish 6β-bromo-Δ⁴-cholesten-3-one, recrystallized from petroleum ether (b. p. 40–60°), m. p. 132°. There was no depression in m. p. on admixture with the 6-bromo-Δ⁴-cholesten-3-one, m. p. 130°, $[\alpha]_D$ + 6° (*c*, 2.17), $[M]_D$ + 28°, obtained by the known procedure[9] from ordinary cholesterol dibromide. Admixture with the 6α-bromo-isomer described below gave a 20° depression in m. p.

5β,6α-Dibromocholestan-3β-ol.—Ordinary cholesterol dibromide (10 g.) was dissolved in 100 ml. of chloroform and left to stand at room temperature for three days. About 50 ml. of the solvent was removed *in vacuo* and the solution was then diluted rapidly with methanol. The first crop of crystals was unchanged starting material. Further dilution with methanol furnished, after recrystallization from ethyl acetate–methanol, pure 5β,6α-dibromocholestan-3β-ol (1. 6 g.), m. p. 143° decomp., $[\alpha]_D$ + 47° (*c*, 1.42), $[M]_D$ + 257°.

Anal. Calcd. for $C_{27}H_{46}Br_2O$: Br, 29.2. Found: Br, 29.8.

5β,6α-Dibromocholestan-3β-yl benzoate, recrystallized from ethyl acetate–methanol, m. p. 163–164° dec., $[\alpha]_D$ + 82° (*c*, 8.33), + 82° (*c*, 6.75), was prepared by leaving a chloroform solution of the "labile" dibromide to stand for three weeks. This preparation was, however, more expeditiously carried out by refluxing in chloroform solution for two hours. Benzoylation of 5β,6α-dibromocholestan-3β-ol in pyridine solution at 0° and leaving for thirty minutes only, also gave the benzoate, identical in all respects with that obtained by rearrangement. 5β,6α-Dibromocholestan-3β-yl benzoate furnished cholesteryl benzoate (identity confirmed by mixed m. p.) on debromination with zinc dust in acetic acid solution in the usual way. An analysis on 5β,6α-dibromocholestan-3β-yl benzoate confirmed the results of Bretschneider, *et al.*[13]

Anal. Calcd. for $C_{34}H_{50}Br_2O_2$: Br, 24.57. Found: Br, 24.9.

Attempts to dehydrobrominate 5β,6α-dibromocholestan-3β-yl benzoate by treatment with various alkaline reagents led either to the recovery of starting material unchanged or to uncrystallizable gums.

Rates of Alkali Consumption of the Cholesteryl Benzoate Dihalides.—As mentioned in the text it was of some importance to determine the rates of consumption of alkali by the cholesteryl benzoate dihalides. Approximately 0.012 *M* solutions of the dihalides in pure, dry dioxane were mixed with an equal volume of 0.0675 *N* methanolic potassium hydroxide and the alkali consumption determined from time to time by acid titration in the usual manner (phenolphthalein as indicator). The necessary blanks, were, of course, run at the same time. The results are expressed on the assumption that each dihalide should consume 2 equivalents of alkali.

-Cholestan-3β-yl benzoate	Molarity	Time	Temp., °C.	Percentage reacted
5α,6β-Dichloro-	0.01258	5 hr.	73	16.8
5α,6α-Dichloro-	.01200	1 hr.	73	13.3
		5 hr.	73	60.1
5α,6β-Dibromo-	.01347	2 days	25	80.8
5β,6α-Dibromo-	.01148	2 days	25	40.7

Rates of Debromination of the Cholesteryl Benzoate Dibromides.—Approximately 0.006 *M* solutions of the two benzoate dibromides in dry acetone were mixed in equal volume with 0.133 *N* sodium iodide in the same solvent. The course of the reaction was followed from time to time by thiosulfate titration of the iodine liberated. The results obtained are summarized in the table below.

-Dibromocholestan-3β-yl benzoate	Molarity	Temp., °C.	Percentage reacted 15 min.	225 min.	15 hr.
5α,6β-	0.00611	5	30.1	69.8	...
5β,6α-	.00662	28	0.0	0.0	6.3

6-α-Bromo-Δ⁴-cholesten-3-one.—5β,6α-Dibromocholestan-3β-ol (500 mg.) was oxidized by chromic acid as for the isomeric ordinary cholesterol dibromide.[5] The reaction product was treated with sodium acetate in alcoholic solution as for the preparation of 6β-bromo-Δ⁴-cholesten-3-one.[9] Crystallization of the product in the *cold* from ethyl acetate–methanol afforded 6α-bromo-Δ⁴-cholesten-3-one, m. p. 113°, $[\alpha]_D$ + 53° (*c*, 1.51), $[M]_D$ + 245°, λ_{max}. 238 mμ, ε = 15,800 (in alcohol).

Anal. Calcd. for $C_{27}H_{43}BrO$: Br, 17.2. Found: Br, 18.2.

On treatment with the 2,4-dinitrophenylhydrazine reagent in the *hot* in the usual way both stereoisomeric 6-bromo-Δ⁴-cholesten-3-ones furnished cholesta-4,6-dien-3-one 2,4-dinitrophenylhydrazone, purified by chromatography over alumina (Savory and Moore, London) and recrystallization from chloroform–methanol.[3] However, in the cold both ketones gave the same orange substance, m. p. 245°, purified in the same way, as was obtained earlier[3] from the two stereoisomeric 6-chloro-Δ⁴-cholesten-3-ones.

Acknowledgment.—We are much indebted to Professor Louis F. Fieser for the interest that he has taken in this work.

Summary

Ordinary (labile) cholesterol dibromide has been shown to have the bromine atoms in the 5α,-6β-configuration. The "stable" cholesterol dibromide, obtained from the ordinary isomer by standing in solution at room temperature, has been proved to possess the 5β,6α-configuration. The mechanism of this rearrangement has been briefly discussed.

The importance of coplanarity of participating atomic centers in E_2 type elimination reactions has been emphasized and illustrated by reference to the behavior of the cholesteryl benzoate dihalides.

LONDON, S. W. 7, ENGLAND RECEIVED OCTOBER 7, 1949