THE JOURNAL OF Organic Chemistry®

Volume 28, Number 4

April 12, 1963

α-Halo Ketones. III.[1] The Epimeric 2,2-Bromochlorocholestan-3-ones and the Stereochemistry of Ketone Halogenation

E. W. WARNHOFF[2]

Department of Chemistry, University of Southern California, Los Angeles, California

Received September 17, 1962

The compound previously reported to be a pure 2-bromo-2-chlorocholestan-3-one has been found to be a mixture of the two C-2 epimers with other minor contaminants. Both epimeric 2-bromo-2-chlorocholestanones have been obtained in 85–90% purity by kinetically controlled halogenation of 2α-chloro- and 2α-bromocholestanone. The stereochemistry, conformation, and relative stability of the two epimers have been determined. Results are discussed in the context of the present view of the stereochemistry of ketone halogenation. The reactions of the epimers with 2,4-dinitrophenylhydrazine, hydrogen bromide, and hydrogen chloride have been examined.

The available evidence[3,4] on the bromination and chlorination of cyclohexanones supports a consistent, if not very detailed, interpretation of the stereochemical course of the reaction. In the absence of marked steric factors which would interfere with entrance of the halogen from one side or other of the enol, addition takes place to give the α-halo ketone with an axial halogen as the predominant (but not necessarily exclusive) initial, kinetically controlled product in those systems incapable of conformational inversion.[5] This isomer may or may not be the thermodynamically more stable one. The reason originally proposed[3] for this selectivity was that the transition state for such a course allowed maximum overlap of the orbital of the positive halogen species and the π orbital of enol–enolate double bond and hence lowest energy of activation for the addition. These views required modification when it was demonstrated that in a number of cases, where steric factors hindered approach to the enol–enolate side leading to an axial halogen in the product, the equatorial α-halo ketone was the major initial, kinetically controlled product.[4] It has been pointed out[6] that in these cases the principle of preferred axial addition to maintain maximum orbital overlap can be retained, if it is postulated that addition to the cyclohexenol occurs to give first a boat conformation axial α-halo ketone. Subsequent conformational adjustment to a chair form would occur if energetically favorable. While the exact nature and geometry of intermediates in the formation of both axial and equatorial α-halocyclohexanones are at present moot points, it is clear that bond formation between the halogen and the cyclohexenol to give the initial, rate-controlled product may occur predominantly from either side of the double bond depending on steric and electronic factors.[7] The situation is illustrated by the rate-controlled halogenation of A/B *trans* 3-keto steroid derivatives.[4,7f,g] Thus 3-keto steroids **1** with the axial C-19 methyl group give the equatorial 2α-chloro or 2α-bromo ketones **2** or **3** (more stable epimers), while those **7** without the C-19 methyl group give mainly the axial 2β-bromo ketone **8** (more stable epimer), and some axial 4β-bromo ketone **9**. Those 3-keto steroids **10** with an equatorial 2α-methyl group in addition to the axial C-19 methyl group give only 2α-bromo-2β-methyl ketones (less stable epimer) which are more stable in the boat conformation **11** than in the chair form; but, if the C-19 methyl group is missing as in **12**, the product is a mixture of comparable amounts of 2β(axial)-bromo-2α-methyl **13** and 2α(equatorial)-bromo-2β-methyl **14** ketones. Introduction of steric hindrance to approach to the underside of the molecule in the form of an axial 5α-halo or methyl substituent in **1** (CH_3, Cl, or Br for 5α-H) reverses the steric course, and these compounds give the less stable axial 2β-bromo derivative as the isolated product.[7f,g]

(1) Part II, *J. Org. Chem.*, **27**, 4587 (1962).

(2) Department of Chemistry, University of Western Ontario, London, Ontario, Canada.

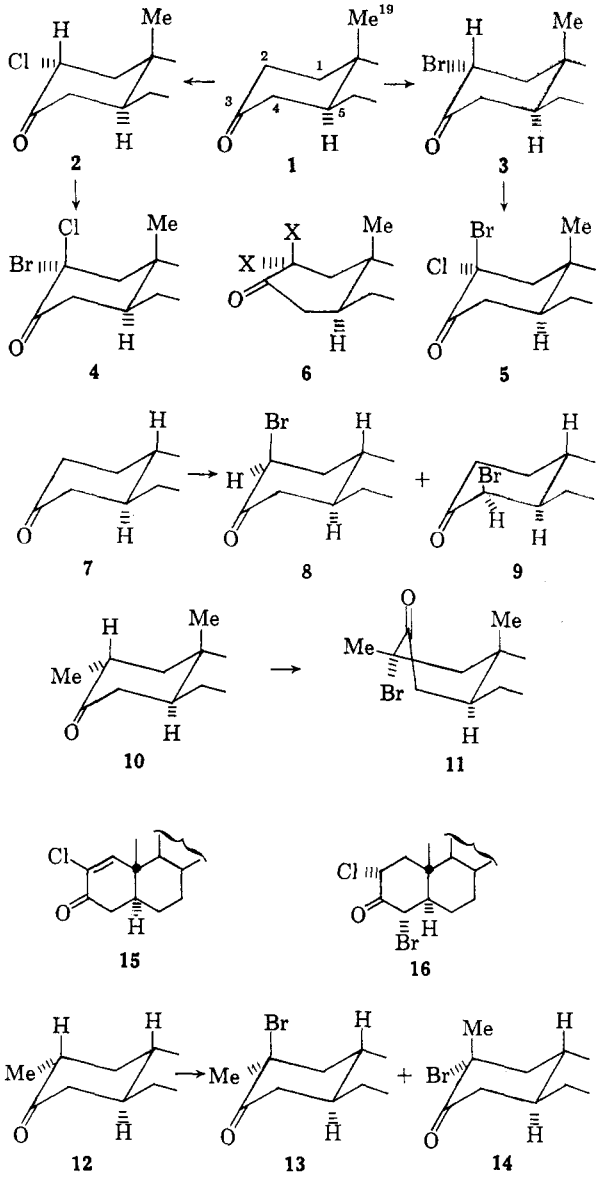
(3) (a) E. J. Corey, *Experientia*, **9**, 329 (1953); (b) E. J. Corey, *J. Am. Chem. Soc.*, **76**, 175 (1954).

(4) R. Villotti, H. J. Ringold, and C. Djerassi, *ibid.*, **82**, 5693 (1960).

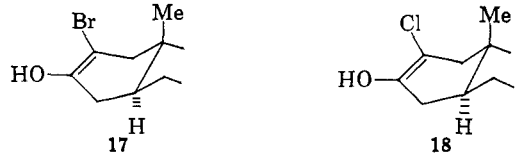
(5) In certain examples the chair conformation of the initial product with an axial α-halogen may be less stable than the boat conformation with an equatorial halogen. See ref. 7.

(6)(a) J. Valls and E. Toromanoff, *Bull. soc chim. France*, 758 (1961); (b) D. H. R. Barton and G. A. Morrison, *Fort. Chem. Org. Nat.*, **19**, 211 (1961).

(7) See, *inter alia* (a) C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *J. Am. Chem. Soc.*, **82**, 5488 (1960); (b) R. Mauli, H. J. Ringold, and C. Djerassi, *ibid.*, **82**, 5494 (1960); (c) G. de Stevens and A. Halamandaris, *Experientia*, **17**, 297 (1961); (d) D. T. Cropp, B. B. Dewhurst, and J. S. E. Holker, *Chem. Ind.* (London), 209 (1961); (e) D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957); (f) J.-C. Jacquesy and J. Levisalles, *Bull. soc. chim. France*, 189 (1962); (g) J.-C. Jacquesy and J. Levisalles, *Chem. Ind.* (London), 1310 (1961).



Whether or not the course of ketone halogenation is that outlined above, one would expect the rate-controlled chlorination of the bromoenol **17** from 2α-bromocholestanone (**3**) and bromination of the chloroenol **18** from 2α-chlorocholestanone (**2**) to give different products (or ratios of products) epimeric at C-2,



provided, as seems likely, the steric effects of chlorine and bromine are comparable. Two groups[8,9] have independently reported that both of these reactions yielded the same pure 2,2-bromochlorocholestanone under conditions which permitted, but did not insure, kinetically controlled reactions. Two possible explanations were offered[8] for this behavior—(a) epimerization of the initial product of one reaction by debromination and rebromination, or (b) prior "rapid halogen exchange" of bromine for chlorine in one reaction. The product was tentatively assigned[8] the structure of 2β-bromo-2α-chlorocholestan-3-one (**5**) on the basis of γ-collidine dehydrohalogenation to 2-chloro-Δ^1-cholesten-3-one (**15**). The elimination of bromine rather than chlorine was felt to signify an axial 2β-bromine for ready *trans* diaxial elimination with the axial 1α-hydrogen provided that ring A reacted in the chair conformation.[10] No evidence was presented for the 2β-bromo-2α-chloro ketone being more stable than the 2β-chloro-2α-bromo isomer. In addition the assumption[8] on which part of the argument was based, that axial halogenation from the β-side invariably occurred, has been disproved by later work.[4]

The criteria of purity and identity reported[8,9] (m.p., mixture m.p., optical rotations, and infrared spectra) were not convincing under the circumstances. It would not be surprising if such closely related compounds as the epimeric 2,2-bromochlorocholestanones had these physical properties almost identical. The two isomers might well have the same crystal structure and hence nearly the same melting points which would give no depression on admixture. For example, 2α,4α-dibromocholestan-3-one and 2α-chloro-4α-bromocholestan-3-one have m.p. 194°, $[\alpha]_D$ +3°, and m.p. 196°, $[\alpha]_D$ +5°, respectively, and give no mixture melting point depression. A number of A-ring dichloro, dibromo, and bromochloro derivatives of cholestane have been found to give no melting point depression on admixture.[12] Although the infrared spectra were reported[8] to be identical, they were recorded in chloroform and carbon tetrachloride which absorb strongly in the 670–850-cm.$^{-1}$ region and would obscure any differences in the carbon–halogen absorption region. Nor did the evidence presented prove that the bromochloro ketones were necessarily pure. In view of this unsatisfactory state of a matter of some theoretical significance the previous work was re-examined.

When the bromination of 2α-chlorocholestanone (**2**) and the chlorination of 2α-bromocholestanone (**3**) were repeated according to the directions of Ellis and Petrow,[9] each reaction gave a product with the properties reported by both groups[8,9] except for slight differences in optical rotation. There was no depression in the melting point on admixture. The two samples gave a single spot with the same R_f value on thin layer chromatography.[13] The ultraviolet spectra were identical, but the infrared spectra in carbon disulfide had one minor but reproducible point of difference. The bromination product exhibited a broad peak at 715 cm.$^{-1}$ while this appeared at 721 cm.$^{-1}$ in the chlorination product. This discrepancy encouraged resort to a more discriminating tool, nuclear magnetic resonance. The epimeric 2-bromo-2-chlorocholestanones would be

(8) J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954).
(9) B. Ellis and V. Petrow, *J. Chem. Soc.*, 3869 (1953).

(10) This argument is weak since ring A can undergo boat–chair interconversion. Regardless of its original conformation, the bromine can become axial in one of the chair or boat forms of ring A. Furthermore, whether the bromine must be axial or not for ready elimination, it would not be unreasonable for bromine, whatever its lowest energy conformation, to be lost more readily than chlorine. For example, reductive removal of axial or equatorial bromine from the *trans*- or *cis*-2-bromo-4-*t*-butylcyclohexanones, respectively, occurs more readily than reductive removal of chlorine from either *cis*- or *trans*-2-chloro-4-*t*-butylcyclohexanone.[11]

(11) A. M. Wilson and N. L. Allinger, *J. Am. Chem. Soc.*, **83**, 1999 (1961).

(12) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4286 (1954).

(13) There were faint traces of three other spots, one of which corresponded to 2α-bromo- or 2α-chlorocholestanone and another to a 2α,4α-dihalocholestanone.

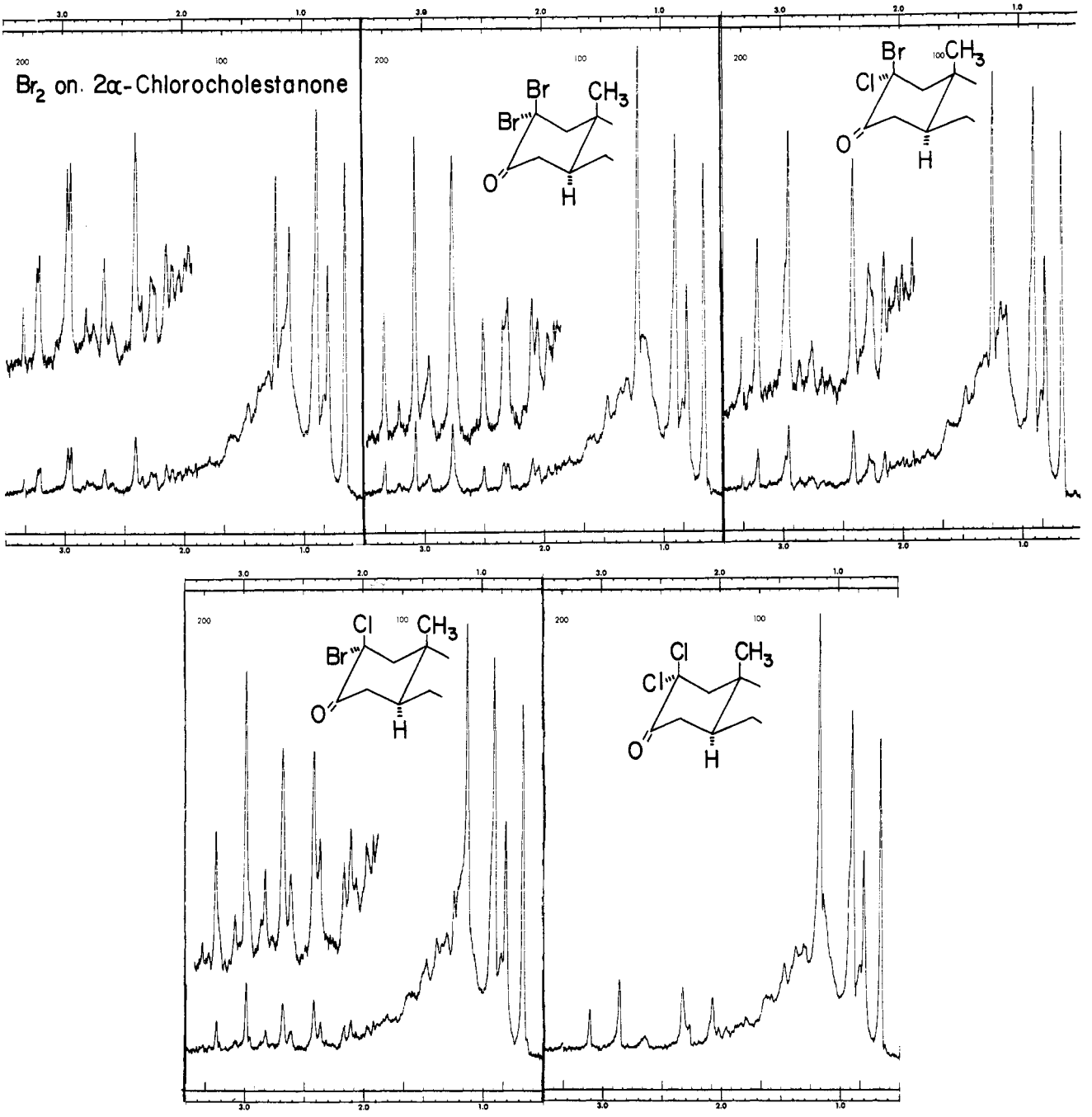


Fig. 1.—Nuclear magnetic resonance spectra of 2,2-dihalocholestan-3-ones.

expected to differ in the chemical shift of the C-1 hydrogens and in the magnetic anisotropy effect of nearby chlorine or bromine on the resonance position of the C-19 methyl group, an effect noted by Shoolery and Rogers.[14] In fact, the nuclear magnetic resonance spectra of the two products were different, particularly in the 1–1.5-p.p.m. (tetramethylsilane = 0) region of C-19 methyl absorption. The bromination product (Fig. 1) had two sharp peaks at 67 and 73.5 c.p.s.,[15] while the chlorination product had four sharp peaks at 67, 70, 72, and 73.5 c.p.s., but none of the peaks was of three hydrogen intensity. With shorter chlorination time the intensity of the 73.5 c.p.s. peak was increased at the expense of the others. The two products were clearly different mixtures of very similar compounds[16]

(14) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5131 (1958); See also R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961).

(15) C-19 Methyl peak positions are given in c.p.s. from tetramethylsilane. The assignment of the low field 3H singlet to the C-19 methyl absorption follows from ref. 14 and the observation that it was the only methyl peak whose position changed in the various A-ring derivatives. In fact, the constancy of the other methyl peaks at 39, 47.5, and 53 c.p.s. served as a convenient internal check for the exact position of the C-19 methyl resonance.

(16) The spectra of the almost pure epimers do not prove that the weak sharp peaks near the strong C-19 methyl peak (and also presumed to be from C-19 methyl groups) are not from small amounts of other relatively slowly interconvertible conformational isomers (in which case the epimers would be more than 85–90% pure). However, this is unlikely since (a) these weaker sharp peaks correspond exactly in position to the C-19 methyl peaks of known derivatives which might be expected to be present, (b) peak ratios vary with halogenation time in the presence of hydrogen halide, and (c) in a number of pure steroids whose spectra have been determined a single sharp C-19 methyl peak has been observed.[14] However, observation of the C-19 methyl resonance under variable temperature conditions might provide a subtle means of studying in steroids and terpenes those cases in which conformational equilibria would exist with appreciable amounts of different A-ring conformers present.

TABLE I

COMPARISON OF PROPERTIES OF THE 2,2-DIHALOCHOLESTAN-3-ONES

Substituted cholestan-3-one		Hot stage m.p., °C.	$[\alpha]^{25}D$, $CHCl_3$	MD	λ_{max}, mμ (ε)	C-19 methyl nuclear resonance, c.p.s. from $SiMe_4$ in CS_2	Infrared C=O cm.$^{-1}$, CS_2 soln.	RD molecular rotation at first extremum
2,2-Dibromo-	21	141–148 dec.	+122°	+662°	*ca.* 300[a] mμ (ε 116)	72	1737	330 mμ, +10,250°
2β-Bromo-2α-chloro-	5	141–149 dec.	+142°	+713°	300 mμ (ε 111)	73.5	1741	329 mμ, +11,250°
2β-Chloro-2α-bromo-	4	145–150 dec.	+92.6°	+464°	297 mμ (ε 76)	67	1742	323 mμ, + 6,450°
2,2-Dichloro-	22	148–153	+114°	+519°	295 mμ (ε 49)	69.5	1745	325 mμ, + 7,750°

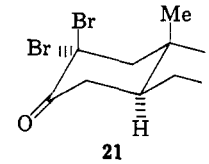
[a] Plateau rather than maximum.

since the nuclear magnetic resonance spectra were not noticeably changed after two further recrystallizations.

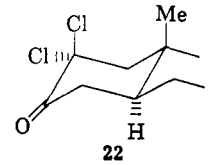
To clarify the course of the halogenations, it was desirable to prepare the two pure 2,2-bromochlorocholestanones. For this purpose it seemed likely that kinetically controlled halogenation of the 2α-halocholestanones might give pure epimers in view of Djerassi's earlier mentioned experience with 2α-methyl-3-keto steroids bearing the C-19 methyl group. If the products obtained[8,9] from halogenation in the presence of the hydrogen bromide or chloride formed were actually mixtures of epimers, they might result from isomerization of pure initial products by the hydrogen halide. Therefore, the procedure[17] used to prepare 2,2-dibromocholestan-3-one (**21**) by rate-controlled bromination of 2α-bromocholestanone in the presence of a large excess of sodium acetate was used. The bromination of 2α-chlorocholestanone and chlorination of 2α-bromocholestanone under these conditions behaved exactly as described for the dibromination.

The two products had the same wide melting range[18] which was not depressed on admixture. Both gave a single spot[13] with the same R_f on thin layer chromatography. However, the nuclear magnetic resonance spectra of the two products (Fig. 1) were distinctly different. In addition to differences in the 2–3-p.p.m. region, each had a strong (*ca.* 3H) C-19 methyl peak, the chlorination product at 73.5 c.p.s. and the bromination product at 67 c.p.s.,[15] contaminated with a small C-19 methyl peak of the other. Determination of the relative areas under the C-19 methyl peaks by the cut-and-weigh technique with reference to the spectrum of cholestan-3-one (C-19 methyl at 58 c.p.s.) for background absorption revealed each epimer to be 85–90% pure.[19] The chlorination epimer was contaminated with about 6% of the other epimer and about 6% of 2,2-dichlorocholestanone (**22**). The bromination epimer was contaminated with about 10% of the other epimer and perhaps 1–2% of 2,2-dibromo ketone.[16] The nuclear magnetic resonance spectra and the optical properties (Table I) proved each to be a 2,2-dihalo ketone and not a 2,4-dihalo ketone. No absorption from the CO-CHX-C group of a 2-halo- or 2,4-dihalocholestanone could be detected in the 4–5-p.p.m. region of the spectra. Any such impurity[13] must be present in very small ($< \sim 3\%$) amount.

The other physical properties—optical rotation, ultraviolet spectra, infrared spectra, and rotatory dispersion—of the two epimers also differed considerably (Table I),[20,21] and by comparison with the same properties of the known 2,2-dichloro- and 2,2-dibromocholestan-3-ones **22** and **21**, respectively, permitted an unambiguous assignment of conformation and stereochemistry.

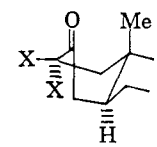


21

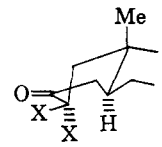


22

The conformation of ring A in each of the four 2,2-dihalo ketones is the same, the rotatory dispersion curves being very similar. Moreover, the fact that the single Cotton effect curve is positive and of the amplitude expected[22,30] for an axial α-halo ketone eliminates either possible boat conformation **19** or **20** or any flexible conformation intermediate between the



19



20

two, since by the axial halo ketone rule,[22] any of these would have a negative Cotton effect. Ring A must then be in the normal chair form **4** and **5**, or perhaps a slightly flattened chair **6** similar to that postulated by Allinger[23] for ring A of 4,4-dimethyl-3-keto steroids. Any flattening cannot be pronounced though, since in the extreme case **23** this would place each halogen in a far octant of opposite sign. The resultant would have been a diminution of amplitude in all four rotatory dispersions and, because the effect of axial bromine is greater than axial chlorine, a different sign of the

(17) C. W. P. Crowne, R. M. Evans, G. F. H. Green, and A. G. Long, *J. Chem. Soc.*, 4351 (1956).

(18) The hot stage melting points of all four of the 2,2-dihalocholestanones have wide ranges which depend on the rate and total time of heating; mixture melting points are not depressed. In the case of **21** evolution of gas (HBr?) takes place on melting. Capillary melting points appear somewhat sharper, probably because the initial melting is not seen. In this series the melting point is useless as a criterion of purity or identity.

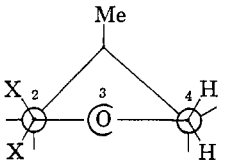
(19) Although the isolated yields of **4** and **5** are not quantitative, the ratio of **4**:**5** in the recrystallized products is probably close to the ratio in which they are formed because **4** and **5** (presumably isomorphous) show no detectable separation (n.m.r. spectrum) on further recrystallization.

(20) The optical rotation, ultraviolet and infrared spectra of Djerassi's and Petrow's bromochloro ketones are intermediate between those found for **4** and **5**.

(21) From the optical rotations and extinction coefficients of the almost pure epimers the following values can be calculated for pure **5**, $[\alpha]D$ +148°, ε 117, and for pure **4**, $[\alpha]D$ +87°, ε 72.

(22) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 115.

(23) N. L. Allinger and M. A. DaRooge, *Tetrahedron Letters*, **19**, 676 (1961); See also J.-M. Lehn, J. Levisalles, and G. Ourisson, *ibid.*, **19**, 682 (1961).



23

Cotton effects of **5** and **4**. Therefore, the β-substituent in these derivatives is axial or nearly so.

Since the optical rotation, rotatory dispersion, ultraviolet spectrum, and (in view of the A-ring conformation) any magnetic anisotropy effect of halogen on the C-19 methyl group will be much more influenced by the axial β-halogen than the equatorial α-halogen,[24] the 2β-bromo-2α-chloro epimer **5** will resemble more closely 2,2-dibromocholestanone, while the 2β-chloro-2α-bromo ketone **4** will resemble more nearly 2,2-dichlorocholestanone. As can be seen from Table I, the molecular rotation, ultraviolet absorption maximum, molecular extinction coefficient, C-19 methyl nuclear resonance position, and rotatory dispersion extremum and amplitude of the product of chlorination of the 2α-bromo ketone **3** are much closer to those of 2,2-dibromocholestanone than 2,2-dichlorocholestanone. Thus it has the 2β-bromo-2α-chloro configuration **5**. Correspondingly, the same properties of the bromination product of the 2α-chloro ketone **2** resemble more nearly those of 2,2-dichlorocholestanone, and it must have the 2β-chloro-2α-bromo stereochemistry **4**.

The infrared spectra provided a complementary check for these assignments. Although the carbonyl frequencies of the bromochloro ketones lay between those of the dichloro and dibromo isomers, they were the same within experimental error. However, examination of that part of the carbon–bromine, carbon–chlorine absorption region (800–500 cm.$^{-1}$) transparent to sodium chloride optics in the four 2,2-dihalo ketones, 2α-chloro- and 2α-bromocholestanone, and cholestanone permitted a consistent assignment of peaks (Fig. 2) to axial or equatorial chlorine or bromine which agrees with the stereochemistry and conformation deduced and with the previous findings on carbon–halogen infrared absorption in steroids.[25]

In principle the relative stability of the two epimers could be determined from observation of the change in intensities of the C-19 methyl resonance peaks at 67 and 73.5 c.p.s. as a function of time during hydrogen halide-catalyzed isomerization experiments. Unfortunately, the C-19 methyl peak of the final isomerization product, 2α-chloro-4α-bromocholestanone (**16**), at 68 c.p.s. made it difficult to find the concentration of **4**. Instead, since isomerization proceeds by debromination to **2** and rebromination,[17] an approximate value for the relative stability was calculated from (a) the ratio of the rates of removal of bromine from each epimer, and

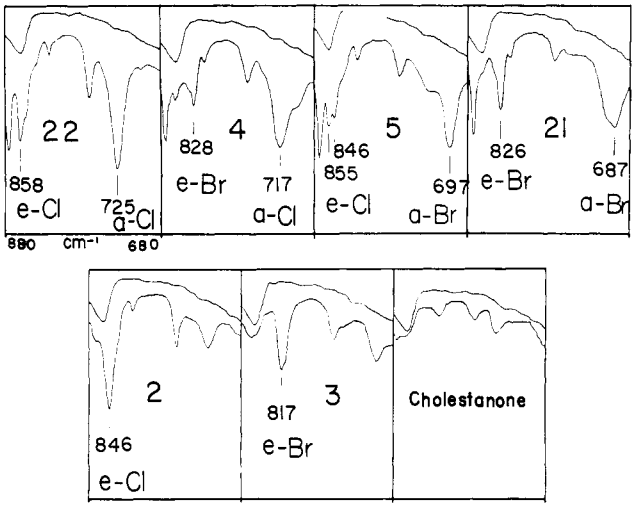
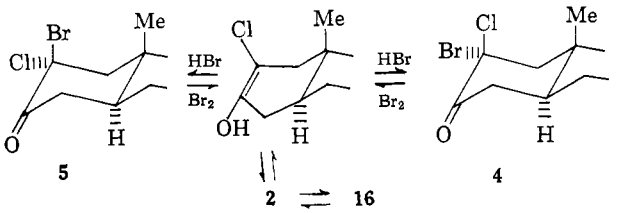


Fig. 2.—Infrared spectra of 2-halogenated cholestan-3-ones in carbon disulfide in the carbon–halogen absorption region. The upper curve in each spectrum is that of pure carbon disulfide. Concn. for each was 20 mg./0.1 ml. in a 0.10-mm. NaCl cell.

(b) the ratio of the rates of halogenation of 2α-chlorocholestanone enol to **4** and **5**. The ratio (b) can be estimated to be about 9, the ratio of **4**:**5** in the product of rate-controlled bromination of chlorocholestanone **2**.[19] The ratio (a) was determined by measuring the relative rates of decrease of the C-19 methyl resonance peaks (the rate of debromination) during hydrogen bromide catalyzed debromination in the presence of β-naphthol as a bromine acceptor[17] to prevent the back reaction or formation of **16**. Under these conditions **4** is debrominated about 2.3 times faster than **5**. These ratios give a



value of about 4 for the equilibrium ratio of **4**:**5**. If this value, admittedly inexact if only because the conditions of the ratio determinations were different, is accepted, the 2β-chloro-2α-bromo epimer is slightly more stable. There is apparently a delicate balance between the greater tendency of chlorine than bromine to assume an equatorial conformation alpha to a ketone[26a] and the greater repulsion of 1,3-diaxial interactions involving bromine in **5** as compared with those involving chlorine in **4**.[26b]

With the stereochemistry, conformation, and relative stability of the 2,2-bromochlorocholestanones settled, the results can be considered in relation to the stereochemistry of ketone halogenation. Both the kinetically controlled bromination of the 2α-chloro ketone **2** and the chlorination of the 2α-bromo ketone **3** are in agreement with the established course of halogenation of 3-keto and 2α-methyl-3-keto steroids. In each case the entering halogen attacks the enol–enolate predominantly (85–90%) from the less hindered α-side, forcing the halogen already present in the ketone into

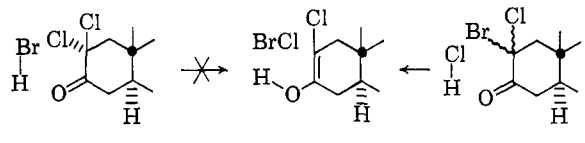
(24) Ultraviolet spectra: R. C. Cookson, *J. Chem. Soc.*, 282 (1954) (From the data in this and other papers axial bromo ketones regularly have higher molecular extinction coefficients than axial chloro ketones.); rotatory dispersion: see ref. 22; optical rotations: L. F. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 287.

(25) D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J. Chem. Soc.*, 331 (1956), have found (a) equatorial bromine (chlorine) to absorb at higher frequencies than axial bromine (chlorine), and (b) equatorial (axial) chlorine to absorb at higher frequencies than equatorial (axial) bromine. The carbon–halogen frequencies of the halocholestanones are not unexpectedly displaced from those reported for the halocholestanes and halocoprostanes.

(26) (a) For a discussion see N. L. Allinger, J. Allinger, L. A. Freiberg, R. F. Czaja, and N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 5876 (1960); (b) see O. Hassel, *Quart. Rev.*, **7**, 227 (1953), and references cited therein.

the axial β-configuration and itself becoming equatorial in the product which has a chair form A-ring. These same products in about the same ratios probably are formed initially under nonkinetically controlled conditions,[8,9] but in the presence of the hydrogen bromide or chloride formed during the reaction, the primary product has ample time for C-2 epimerization by hydrogen halide-catalyzed reductive debromination and rebromination as well as rearrangement to 2α-chloro-4α-bromocholestanone (**16**). Evidence for this view is the greater proportion of **5** formed in chlorinations of **3** with shorter reaction times. Also each epimer **4** and **5** undergoes these changes in the presence of either hydrogen bromide or chloride under conditions (see Experimental) approximating those of the *nonkinetically controlled halogenations*.[8,9] The halogen removed from each epimer is bromine since dehalogenations in the presence of a trapping agent (β-naphthol) gave almost pure 2α-chlorocholestanone **2** in each case.

The fact that hydrogen chloride catalyzes the debromination of **4** and **5** (see Experimental) prompted reinvestigation of the report[17] that the closely related 2,2-dibromocholestanone (**21**) was unchanged by hydrogen chloride in acetic acid. Lack of reactivity was judged by no change in the optical rotation over an unspecified period of time.[27] In our hands the dibromo ketone does slowly rearrange at room temperature in the presence of hydrogen chloride in acetic acid to 2α,4α - dibromocholestanone accompanied by some monobromo ketone **3**. On the other hand 2,2-dichlorocholestanone is unaffected by hydrogen bromide[8] or chloride in acetic acid. It would appear that in general a ketonic α-bromine may be reductively removed by either hydrogen bromide or chloride, but an α-chloro ketone is not subject to reduction by either reagent. In the reactions of **4** or **5** with hydrogen chloride and **22** with hydrogen bromide the same bonds are formed. The only significant difference is the carbon–halogen bond broken since both hydrogen halides catalyze the debromination. The reason for the failure of the dechlorination reaction must reside in the greater strength of the carbon–chlorine as compared with the carbon–bromine bond. Differences in steric repulsion of the C-19 methyl group for axial chlorine *vs.* bromine cannot be a major factor in the failure of the dechlorination of **22** since **4** is readily debrominated.



Djerassi has reported[8] that his bromochloro compound on reaction with 2,4-dinitrophenylhydrazine gave only the 2,4-dinitrophenylhydrazone of 2-chloro-Δ^1-cholesten-3-one (**15**). The reaction of both bromochloro ketones **4** and **5** with the reagent has also been found to give this same derivative contaminated with about 3% of the 2-bromo-Δ^1-cholesten-3-one derivative. Whether the small amount of bromo derivative came from **4** or **5** or from traces of 2,2-dibromo ketone in **4** and **5**, the preponderant course of the reaction was dehydrobromination. This apparent lack of steric preference in the Kendall–Mattox reaction may not be real in view of the conformational mobility of ring A and the fact that bromine is a much better leaving group than chlorine.[10]

(27) 2,2-Dibromocholestanone was not soluble enough in the acetic acid–hydrogen chloride solution for preparation of a 0.5% (w./v.) solution as used in ref. 17 unless the mixture were stirred long enough to permit isomerization.

Experimental

General procedure and instruments are the same as in parts I and II.[1,28] Nuclear magnetic resonance spectra were recorded on a Varian A-60 instrument in carbon disulfide solution with tetramethylsilane (=0) as an internal standard. Accurate carbonyl frequencies were measured in carbon disulfide on a Beckman IR-7 infrared spectrophotometer. Rotatory dispersion measurements were carried out on absolute ethanol solutions on a Rudolph photoelectric polarimeter. Each set of physical measurements (optical rotations, ultraviolet spectra, infrared spectra, and rotatory dispersions) on **4**, **5**, **21**, and **22** was taken on all four compounds at one time to eliminate instrument variation. Analyses were by J. F. Alicino, Metuchen, N. J.

Reagents.—(a) 2α-Bromocholestan-3-one (**3**), m.p. 168–170° (capillary), was prepared by bromination of cholestan-3-one according to the procedure of Fieser and Dominguez.[29]

(b) 2α-Chlorocholestan-3-one (**2**), m.p. 180–185° (capillary) was prepared by chlorination of cholestan-3-one according to the procedure of Ellis and Petrow.[9]

(c) 2,2-Dichlorocholestan-3-one (**22**), m.p. 148–153°, $[\alpha]^{25}D$ +114° (*c*, 2.15 in chloroform), $\lambda_{max}^{EtOH:CHCl_3(4:1)}$ 295 mμ (ϵ 49) (reported,[9] m.p. 151–152°, $[\alpha]D$ +115°), was made in 53% yield by chlorination of 2α-chlorocholestanone following the directions of Ellis and Petrow.[9]

Rotatory dispersion[30]: absolute ethanol (*c*, 0.0615), 24°, $[\alpha]_{589}$ +102°, $[\alpha]_{325}$ +1847°, $[\alpha]_{315}$ +1606°.

(d) 2,2-Dibromocholestan-3-one (**21**), m.p. 141–148° dec. $[\alpha]^{25}D$ +122° (*c*, 2.34 in chloroform), $\lambda_{inflection-plateau}^{EtOH:CHCl_3(4:1)}$ 300 mμ (ϵ 116) (reported,[17] m.p. 153–158°, $[\alpha]D$ +116°) was prepared in 63% yield by bromination of 2α-bromocholestanone in the presence of excess potassium acetate according to Crowne, *et al.*[17]

Rotatory dispersion[30]: absolute ethanol (*c*, 0.0635), 24°; $[\alpha]_{589}$ +94°, $[\alpha]_{330}$ +1889°, $[\alpha]_{320}$ +1530°.

(e) Solutions of chlorine in glacial acetic acid were prepared immediately before use. Chlorine content was determined by addition of an aliquot of the solution to potassium iodide solution and titration of the iodine liberated with standard thiosulfate solution.

Bromination of 2α-Chlorocholestanone.—The procedure of Ellis and Petrow[9] was used. To a solution of 3.64 g. (8.65 mmoles) of 2α-chlorocholestanone in 50 ml. of chloroform and 50 ml. of glacial acetic acid was added a solution of 1.52 g. (9.5 mmoles) of bromine in 10 ml. of glacial acetic acid. After 45 min. the bromine color was discharged. The solution was poured into an excess of aqueous sodium acetate and the product extracted with ether. The water-washed and dried ether–chloroform solution was evaporated to leave 4.82 g. of gummy solid which was recrystallized three times from ethyl acetate–methanol to give 720 mg. (16%) of colorless prisms, m.p. 143–150° with previous sintering, $[\alpha]^{25}D$ +121° (*c*, 2.03 in chloroform), $\lambda_{max}^{EtOH:CHCl_3(4:1)}$ 298 mμ (ϵ 99) (reported,[8,9] m.p. 145–147°, $[\alpha]D$ +112°).

Chlorination of 2α-Bromocholestanone.—(a) The procedure of Ellis and Petrow[9] was used. To a solution of 6.00 g. (11.7 mmoles)[31] of 2α-bromocholestanone in 60 ml. of chloroform and 60 ml. of glacial acetic acid was added 13 ml. of a solution containing 79 mg. of chlorine/ml. (1.03 g., 14.5 mmoles). The reaction mixture was allowed to stand overnight and then was worked up as for the bromination of **2** described above. The 6.48 g. of crude gummy product was recrystallized from ethyl acetate–methanol to give 1.65 g. of colorless prisms, m.p. 130–141°. Three more recrystallizations gave material of m.p.

(28) E. W. Warnhoff and P. Na Nonggai, *J. Org. Chem.*, **27**, 1186 (1962).

(29) L. F. Fieser and X. A. Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953).

(30) The rotatory dispersion of **21** in dioxane and of **22** in methanol are reported in C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *ibid.*, **80**, 1216 (1958).

(31) Corrected for cholestanone content.[1]

TABLE II

REACTIONS OF 2,2-DIHALOCHOLESTAN-3-ONES WITH HYDROGEN BROMIDE AND CHLORIDE

Exp.	Compound		Wt., mg.	Ml., $CHCl_3$	Ml. HOAc soln. of HX	Reaction time, hr.	Yield product, mg.	Composition of product[a]
a	2,2-Di Cl	**22**	200	4	1 HBr	2.5	182	Pure **22**
b	2,2-Di Cl	**22**	160	3	0.75 HCl	4	149	Pure **22**
c	2,2-Di Br	**21**	200	4	1 HCl	17	193	**16** (Br for Cl)(major), **21**, **3**
d	2,2-Di Br	**21**	107	..	15 HCl	2	104	**21** (mostly), **16** (Br for Cl), **3**
e	2β-Br, 2α-Cl	**5**	150	3	0.75 HBr	2	150	**16** (mostly), **5**, **4**, **2**
f	2β-Br, 2α-Cl	**5**	150	3	0.75 HCl	17	137	**5**, **16**, **4**, **2**
g	2β-Br, 2α-Cl	**5**	100	..	20 HCl	2.6	100	**5**, **16**, **4**, **2**
h	2β-Cl, 2α-Br	**4**	85	1.7	0.45 HBr	2	85	**16** (mostly), **5**, **4** and **2**
i	2β-Cl, 2α-Br	**4**	100	2	0.50 HCl	2	96	**4**, **16**, **5**
j	2α-Br	**3**	105	2	0.5 HBr	4.3	113	Starting material **3**

[a] From inspection of n.m.r. spectrum of total crude product compared with that of starting material.

145–148° with previous sintering, $[\alpha]^{25}D$ +128° (*c*, 2.35 in chloroform), $\lambda_{max}^{EtOH:CHCl_3(4:1)}$ 298 mμ (ε 99) (reported,[8,9] 147–148°, $[\alpha]D$ +112.5° (*c*, 1.45), $[\alpha]D$ +117°).

(b) The reaction was repeated on 1.112 g. (2.17 mmoles)[31] of **3** in 10 ml. of chloroform and 7 ml. of glacial acetic acid for only 1 hr. after the addition of a solution of 174 mg. (2.45 mmoles) of chlorine in 6 ml. of glacial acetic acid. The crude product (1.193 g.) gave 392 mg. (36%) of colorless prisms after two recrystallizations from ethyl acetate–methanol, $[\alpha]^{26}D$ +140° (*c*, 2.50 in chloroform).

2α-Bromo-2β-chlorocholestan-3-one (**4**).—The procedure of Crowne, *et al.*,[17] for the preparation of **21** was modified. A hot (90°) solution of 3.29 g. (32.9 mmoles) of freshly oven-dried (110°) potassium acetate in 13 ml. of glacial acetic acid was added to a hot (90°) solution of 747 mg. (1.77 mmoles) of 2α-chlorocholestanone in 25 ml. of glacial acetic acid on the steam bath. Immediately afterward a solution of 504 mg. (3.14 mmoles) of bromine in 5 ml. of glacial acetic acid was added. The reaction mixture was left on the steam bath until the bromine color was discharged after 15 min. The flask was then cooled to room temperature in an ice bath. Spontaneous crystallization deposited 467 mg. (53%), m.p. 140–147° dec., after filtration and washing with acetic acid and water. Two recrystallizations from ethyl acetate–methanol gave large colorless prisms, m.p. 145–150° dec., $[\alpha]^{25}D$ +92.6° (*c*, 2.19 in chloroform), $\lambda_{max}^{EtOH:CHCl_3(4:1)}$ 297 mμ (ε 76), $\lambda_{max}^{CS_2}$ 1742 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{27}H_{44}OBrCl$ (500.02): C, 64.85; H, 8.87; Br, 15.98; Cl, 7.09. Found: C, 64.91; H, 8.78; Br, 16.25; Cl, 7.19.

Rotatory dispersion: absolute ethanol (*c*, 0.112), 25°; $[\alpha]_{589}$ +72°, $[\alpha]_{323}$ +1290°, $[\alpha]_{315}$ +1096°.

2α-Chloro-2β-bromocholestan-3-one (**5**).—The procedure of Crowne, *et al.*,[17] for the preparation of **21** was modified. To a hot (90°) solution of 2.03 g. (3.92 mmoles)[31] of 2α-bromocholestanone in 70 ml. of glacial acetic acid on the steam bath was added a hot (90°) solution of 7.40 g. (74 mmoles) of freshly oven-dried (110°) potassium acetate in 30 ml. of glacial acetic acid followed immediately by addition of 10 ml. of a glacial acetic acid solution of chlorine containing 56 mg./ml. (560 mg., 7.9 mmoles). The reaction mixture was left on the steam bath for 20 min. at which time a faint yellow color persisted. Then the flask was cooled to room temperature in an ice bath. Crystallization was initiated by scratching and yielded 1.306 g. (66%), m.p. 143–148° dec., after filtration and washing with acetic acid and water. Two recrystallizations from ethyl acetate–methanol gave large colorless prisms, m.p. 141–149° dec., $[\alpha]^{25}D$ +142° (*c*, 2.20 in chloroform), $\lambda_{max}^{EtOH:CHCl_3(4:1)}$ 300 mμ (ε 111), $\lambda_{max}^{CS_2}$ 1741 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{27}H_{44}OBrCl$ (500.02): C, 64.85; H, 8.87; Br, 15.98; Cl, 7.09. Found: C, 64.96; H, 8.82; Br, 15.88; Cl, 7.14.

Rotatory dispersion: absolute ethanol (*c*, 0.080), 25°; $[\alpha]_{589}$ +135°, $[\alpha]_{329}$ +2250°, $[\alpha]_{320}$ +1950°.

2,4-Dinitrophenylhydrazones: General Procedure.—A mixture of 50 mg. (0.092–0.11 mmole) of 2,2-dihalo ketone and 25 mg. (0.12 mmole) of 2,4-dinitrophenylhydrazine was heated with 4 ml. of glacial acetic acid on the steam bath. The solids dissolved and derivative precipitated in 1–2 min. After further heating, the acetic acid was removed by centrifugation and decantation. The orange precipitate was washed once with 2 ml. of acetic acid, twice with water, dried, weighed, and recrystallized.[32]

(a) 2,2-Dichlorocholestanone (**22**) gave 60 mg. (91%) of crude derivative, m.p. 268–271° dec. Recrystallization from chloroform gave 51 mg. of orange blades of **2-chloro-Δ¹-cholesten-3-one 2,4-dinitrophenylhydrazone**, m.p. 274-276° dec. (reported,[33] m.p. 273–275°), $\lambda_{max}^{CHCl_3}$ 373 mμ (ε 25,000).

(b) 2,2-Dibromocholestanone (**21**) gave 56 mg. (96%) of crude derivative, m.p. 263–267° dec. Recrystallization from chloroform gave 30 mg. of orange blades of **2-bromo-Δ¹-cholesten-3-one 2,4-dinitrophenylhydrazone**, m.p. 273-275° dec. (reported,[34] 265–267° dec.), $\lambda_{max}^{CHCl_3}$ 375 mμ (ε 28,400). The mixture melting point of the 2-chloro- and 2-bromo- derivatives was 272–274° dec.

(c) 2α-Bromo-2β-chlorocholestanone (**4**) gave 46 mg. (77%) of crude derivative, m.p. 269–272° dec. Recrystallization from chloroform gave 36 mg. of orange blades of almost pure **2-chloro-Δ¹-cholesten-3-one 2,4-dinitrophenylhydrazone**, m.p. 273–276° dec., $\lambda_{max}^{CHCl_3}$ 374 mμ (ε 31,000).

Anal. Calcd. for $C_{33}H_{47}N_4O_4Cl$ (599.22): Cl, 5.91. Found[35]: Cl, 5.77; Br, 0.5.

(d) 2α-Chloro-2β-bromocholestanone (**5**) gave 49 mg. (82%) of crude derivative, m.p. 269–272° dec. Recrystallization from chloroform gave 38 mg. of orange blades of almost pure **2-chloro-Δ¹-cholesten-3-one 2,4-dinitrophenylhydrazone**, m.p. 272–274° dec., $\lambda_{max}^{CHCl_3}$ 375 mμ (ε 30,000).

Anal. Calcd. for $C_{33}H_{47}N_4O_4Cl$ (599.22): Cl, 5.91. Found[35]: Cl, 5.72; Br, 0.5.

Thin Layer Chromatography.—On silica gel plates developed with ethyl acetate: cyclohexane (2:98) the following R_f values were obtained: **4**, 0.47; **5**, 0.47; mixture of products from chlorination of **3**, 0.50; and mixture of products from bromination of **2**, 0.50; **21**, 0.48; **22**, 0.48; **1**, 0.12; **2**, 0.12; **3**, 0.17; and **16**, 0.00–0.04. Single dark spots were obtained with very faint traces along the migration path and faint spots at each origin (except for **1**, **2**, and **3**).

Isomerizations.—(See Table II.) Each reaction was conducted at room temperature in acetic acid or chloroform–acetic acid solution in the presence of hydrogen bromide or hydrogen chloride. Each was worked up by pouring into a large excess of aqueous sodium acetate. The product was extracted with ether and the ether solutions was washed with water, dilute sodium bicarbonate solution, and dried over magnesium sulfate. Filtration and evaporation left the crude product. The stock hydrogen bromide solution contained 23 mg. of anhydrous hydrogen bromide per ml. of glacial acetic acid; the stock hydrogen chloride solution contained 29 mg. of anhydrous hydrogen chloride per ml. of glacial acetic acid.

The products from parts e, f, g, and h were combined, redissolved in acetic acid–chloroform–hydrogen chloride, and allowed to stand for 1 day. Work-up gave 404 mg. of crude product which was recrystallized thrice from chloroform–methanol to give 67 mg. of 2α-chloro-4α-bromocholestan-3-one (**16**), m.p. 187–189° dec. (reported,[8] m.p. 195–196°). The mixture melting

(32) Recrystallization probably did not fractionate the bromo and chloro dinitrophenylhydrazones since these are apparently isomorphous (same melting point and no mixture melting point depression).

(33) J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 3500 (1953).

(34) C. Djerassi, *ibid.*, **71**, 1008 (1949).

(35) Bromine was determined directly [J. F. Alicino, A. Crickenberger, and B. Reynolds, *Anal. Chem.*, **21**, 755 (1949)]. Chlorine was determined by subtracting bromine content from total halogen.

point with a specimen of 2α,4α-dibromocholestan-3-one, m.p. 190–192.5° dec., was 184–190° dec., undepressed.

Debromination of the Bromochlorocholestanones.—(a) A solution of 200 mg. (0.40 mmole) of **5** and 63 mg. (0.43 mmole) of freshly recrystallized 2-naphthol in 5 ml. of carbon disulfide was treated with 1 ml. of glacial acetic acid containing 22 mg. of hydrogen bromide. After 3.5 hr. at room temperature, the reaction mixture was diluted with ether and washed successively with water, dilute sodium bicarbonate solution, dilute sodium hydroxide solution, and saturated sodium chloride solution. The dried organic solution was evaporated to leave 157 mg. (93%) of **2α-chlorocholestanone**. One recrystallization from chloroform–methanol gave 117 mg., m.p. 184–185° (cap.) (reported,[9] m.p. 185–186°), whose infrared spectrum in carbon disulfide (20 mg./0.1 ml.) was identical with that of authentic 2α-chlorocholestanone.

Anal. Calcd. for $C_{27}H_{45}OCl$ (421.09): Cl, 8.43. Found[35]: Cl, 8.57; Br, 0.71.[37]

Acidification of the sodium hydroxide washes and extraction with ether gave 82 mg. which was recrystallized from petroleum ether. There was obtained 14 mg. of 1-bromo-2-naphthol, m.p. 81–83.5° (reported,[36] m.p. 84°).

(b) A 200-mg. (0.40 mmole) sample of **4** was treated exactly as in part (a) except the reaction time was 4 hr. Work-up as described in (a) gave 162 mg. (96%) of crystalline **2α-chlorocholestanone**. One recrystallization from chloroform–methanol yielded 128 mg., m.p. 185.5–186.5° (cap.), whose infrared spectrum in carbon disulfide (20 mg./0.1 ml.) was identical with that of authentic 2α-chlorocholestanone.

Anal. Calcd. for $C_{27}H_{45}OCl$ (421.09): Cl, 8.43. Found[35]: Cl, 7.86; Br, 1.29.[37]

(36) A. J. Smith, *J. Chem. Soc.*, **35**, 789 (1879).

(37) The small amount of bromine is probably from 2α-bromocholestanone present as a contaminant in the starting material **4** or **5**, or formed from **21** (small amount present in **4**) by debromination.

Acidification of the sodium hydroxide washes and extraction with ether gave 77 mg. which was recrystallized from petroleum ether. There was obtained 31 mg. of 1-bromo-2-naphthol, m.p. 78–82°.

Relative Rates of Debromination of 4 and 5.—A solution of 90 mg. (0.18 mmole) of **4** or **5** and 27 mg. (0.187 mmole) of freshly recrystallized 2-naphthol in 0.50 ml. of carbon disulfide was pipetted into a solution of 0.35 mg. of hydrogen bromide in 0.10 ml. of carbon disulfide contained in an n.m.r. sample tube. The spectrum of the capped tube (temperature = 37°) was recorded periodically over the region of C-19 methyl absorption (sweep width 250 cycles, sweep time 250 sec., spectrum amplitude 16, filter bandwidth 1, radio frequency 0.16). The 2-naphthol caused a 3 c.p.s. upfield shift of the C-19 methyl peak of both **4** and **5**. The area under the diminishing C-19 methyl peak was determined by the cut-and-weigh technique. The debromination was treated as a pseudo first-order reaction since the hydrogen bromide concentration will remain constant. First-order rate constants were determined graphically from a plot of log weight of C-19 methyl peak *vs.* time elapsed. The ratio k_4/k_5 obtained in this manner was 2.3. As a check the ratio of the rates of appearance of the C-19 methyl peak of 2α-chlorocholestanone was determined in the same way and found to be 2.5.

Acknowledgment.—The author wishes to thank the National Science Foundation for support under grant G15752 and for a generous departmental grant G18795 toward the purchase of the nuclear magnetic resonance spectrometer, without which this work could not have been done. He also wishes to thank Dr. R. J. Highet and Mrs. K. Warren, National Heart Institute, Bethesda, Maryland, for the rotatory dispersion measurements.

Synthesis of the Five Diastereomeric 1,2,4,5-Cyclohexanetetrols. Nuclear Magnetic Resonance Configurational Proofs[1,2]

G. E. McCasland,[3] Stanley Furuta, L. F. Johnson,[4] and J. N. Shoolery[4]

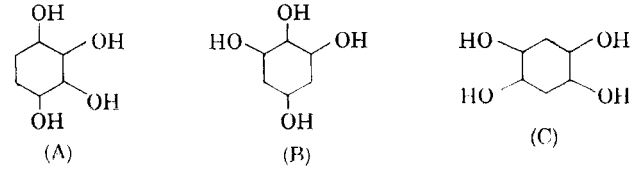
The Institute of Chemical Biology, University of San Francisco, San Francisco 17, and Varian Associates, Palo Alto, California

Received October 29, 1962

The five predicted diastereomers of 1,2,4,5- or "*para*" cyclohexanetetrol have now all been synthesized, and their configurations established by means of nuclear magnetic resonance spectra. *cis*-Hydroxylation of 1,4-cyclohexadiene gave a mixture of the two *cis/cis* tetrols, m.p. 225 and 241°; *trans*-hydroxylation, the two *trans/-trans* tetrols, m.p. 208 and 285°. N.m.r. spectra revealed that the 241 and 208° diastereomers each have four equivalent methylene protons, and so must have the configurations *meso*(12/45) and DL(14/25), respectively. The 225 and 285° diastereomers must then have the remaining configurations *meso*(1245) and *meso*(15/24), respectively. Successive *trans*- and *cis*-hydroxylation gave a tetrol, m.p. 209°, for which only the *cis/trans* configuration DL(124/5) is possible. Conformations are discussed. Acetate and benzoate derivatives were prepared.

In recent publications[2,5] we have reported the use of nuclear magnetic resonance spectra for establishing the configurations and conformations of newly synthesized stereoisomers of dimercaptocyclohexanetetrol and cyclohexanepentol (quercitol). We have now extended this approach to the cyclohexanetetrols[6] (deoxyquercitols).

A cyclohexanepentol or cyclohexanehexol can have various configurations, but only one *structure*. To characterize a cyclohexanetetrol, however, both structure and configuration must be established. The three possible structures for the tetrols are 1,2,3,4- or *ortho* (A); 1,2,3,5- or *meta* (B); and 1,2,4,5- or *para* (C).[7]



(A) (B) (C)

(1) Presented before the Division of Carbohydrate Chemistry at the 143rd National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) Paper XIV on Cyclitol Stereochemistry by G. E. McCasland and coworkers; for preceding paper see *J. Org. Chem.*, **28**, 456 (1963).

(3) To whom any correspondence should be addressed: Institute of Chemical Biology, University of San Francisco, San Francisco 17, Calif.

(4) Varian Associates.

(5) G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, (a) *J. Am. Chem. Soc.*, **83**, 2335 (1961); (b) **83**, 4243 (1961).

(6) The similar problem of preparing cyclopentanetetrols has recently been undertaken. See H. Sable and T. Posternak, Abstracts, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 6-D; see also Y. Gaoni, *Bull. Soc. Chim.*, 705 (1959), and note error in proposed configuration of tetrol, m.p. 137°.

(7) Disubstituted cyclohexanes can be described by the benzene prefixes *ortho*, *meta*, and *para*, and it is convenient to use these same prefixes to specify location of the methylene groups in tetrasubstituted cyclohexanes.