[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

SYNTHESIS AND REACTIONS OF MIXED BROMO-CHLORO 3-KETOSTEROIDS[1]

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Our recently reported study (1) of chlorinated 3-ketosteroids, particularly of the 5α(allo) series, has demonstrated a marked difference in the behavior of these chloro ketones as compared to their bromo and iodo analogs towards reagents such as sodium iodide, collidine, and chromous chloride. It appeared of interest, therefore, to extend this investigation to mixed bromo-chloro 3-ketosteroids which should lend themselves to interesting, selective manipulations and the present paper is concerned with a description of such experiments. Since completion of this manuscript, there has come to our attention a very recent communication by Ellis and Petrow (2) bearing on the same subject. Wherever the work of the British workers parallels that of our past (1) and present papers, the results are in good agreement.

In our hands, the best synthesis of 2α-chlorocholestan-3-one (II) involved chlorination of cholestan-3-one with *tert*-butyl hypochlorite (1). Only traces of a dichloro derivative could be isolated in this reaction in spite of the use of a large excess of the chlorinating agent. We had assigned earlier (1) the 2,2-dichloro formulation (I) to this compound on the basis of its high positive rotation, analogous to that exhibited by 2,2-dibromo-3-keto allo steroids (3–5), and of the ultraviolet absorption spectum of its reaction product (VIIIb) with 2,4-dinitrophenylhydrazine which resembled closely that of the corresponding Δ^1-2-bromo derivative (6). It has now been possible to syntheize this 2,2-dichloro ketone I in much better yield by chlorination of 2α-chlorocholestanone (II) in acetic acid with chlorine gas in the presence of hydrogen chloride. The substance proved to be identical with the earlier described (1) by-product from the *tert*-butyl hypochlorite chlorination of cholestanone. Of interest is the observation that while 2α-chlorocholestanone (II) was resistant to collidine (1), the 2,2-dichloro derivative could be dehydrochlorinated with this reagent to yield Δ^1-2-chlorocholesten-3-one (VIIIa) with an ultraviolet absorption maximum at 246 mμ. The bathochromic effect of the chlorine atom (16 mμ) is notably smaller than that of a bromine atom (*ca.* 25 mμ) (7). Treatment of VIIIa with 2,4-dinitrophenylhydrazine yielded the same dinitrophenylhydrazone (VIIIb) obtained earlier (1) by direct treatment of the 2,2-dichloro-3-ketone (I) with this reagent. While dinitrophenylhydrazones of Δ^1-2-halo-3-ketosteroids can be cleaved to the parent ketone in only poor yield with pyruvic acid (8), we have now observed that Demaecker and Martin's procedure (9)[3] is quite suitable and furnished 75%

[1] From part of the Ph.D. Dissertation of J. J. Beereboom.

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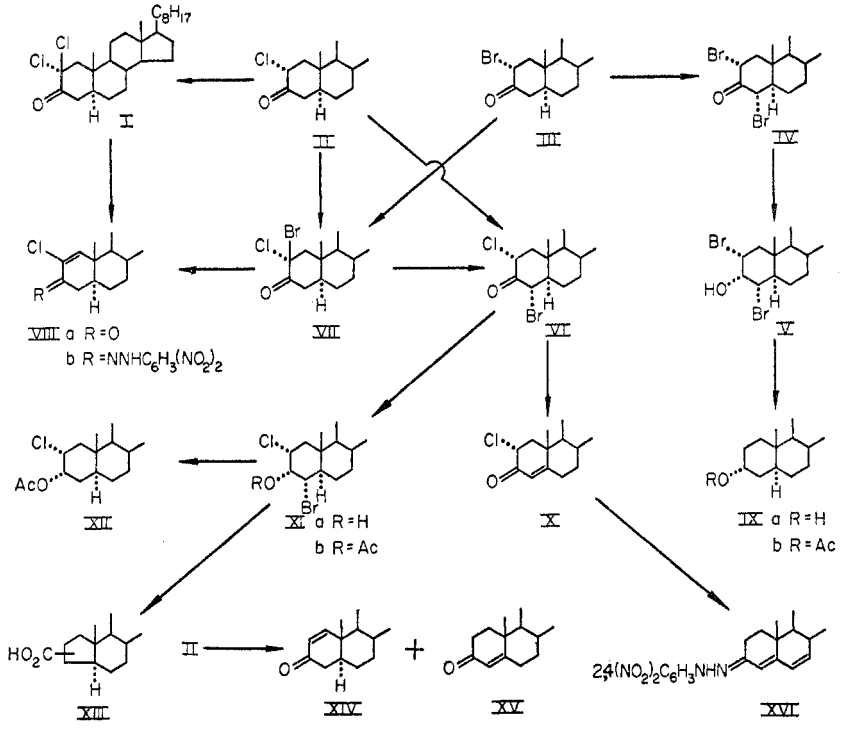
[3] We are greatly indebted to Prof. R. H. Martin of the University of Brussels for this information.



of the Δ^1-2-chloro ketone VIIIa from its 2,4-dinitrophenylhydrazone (VIIIb). [The relatively facile dehydrochlorination of 2,2-dichlorocholestanone (I) with collidine as compared to the resistance of the equatorial monochloro ketone II towards this reagent is probably a manifestation of the combined effects of (a) the easier elimination in a *gem*-dihalo ketone and (b) the fact that one of the chlorine atoms must possess the favorable axial (10) orientation for elimination.] In contrast to the ready rearrangement of 2,2-dibromo-3-ketosteroids to the 2,4-dibromo isomers (IV) in the presence of hydrogen bromide (3–5), the 2,2-dichloro analog I was recovered completely unchanged. The same results were obtained in the androstane-3,17-dione series and we have so far been unable to synthesize a 2,4-dichloro-3-keto steroid.

Recently (11), there was described a new method for the dehydrohalogenation of 4-halodihydrocortisone acetate to cortisone acetate with lithium chloride or bromide in dimethylformamide solution. It seemed appropriate to investigate the behavior of a 2-chloro derivative with these reagents and when 2-chlorocholestanone (II) was subjected to such conditions, a mixture of Δ^1- (XIV) and Δ^4-cholesten-3-one (XV) was isolated in yields of 43 and 31% respectively.

We next turned to the synthesis of the mixed bromochloro ketones. Since it had been established recently that the halogen atom in both 2-chloro-(1) and 2-bromo-cholestanone (12, 13) is equatorial (α-configuration), it was anticipated that bromination of 2α-chlorocholestanone (II) would yield 2β-bromo-2α-chlorocholestanone (VII) while chlorination of 2α-bromocholestanone would lead to

2α-bromo-2β-chlorocholestanone. In fact, both reaction sequences furnished one and the same product which appears to be the 2β-bromo-2α-chloro isomer VII on the basis of the following observations. The high positive rotation and the infrared band at 5.74 μ (14) indicated a *gem*-dihalide structure and this was confirmed by treatment with 2,4-dinitrophenylhydrazine, which furnished in high yield the previously described (1) Δ^1-2-chlorocholestenone dinitrophenylhydrazone (VIIIb). While this reaction is of no stereochemical significance since dehydrohalogenation with 2,4-dinitrophenylhydrazine presumably does not require (15) an axially-oriented halogen atom, collidine treatment of VII also resulted in elimination of hydrogen bromide and the formation of Δ^1-2-chlorocholestenone (VIIIa). Since in this case, di-axial elimination is preferred, it appears likely that the bromine atom in VII possesses the axial orientiation (β). Such an argument is based on the tacit assumption that ring A in the 2,2-dihalo-3-keto allo steroids is still in the chair conformation, an assumption which may not necessarily be valid since the very considerable steric repulsion between a 2β-bromine atom and the angular methyl group at C-10 might force ring A into a boat conformation. Indeed, the change from a boat conformation in 2,2-dihalo ketones to the chair form in the 2α,4α-dihalo ketones (IV, VI) may be one of the important contributing factors in the driving force of the acid-catalyzed rearrangement of such *gem*-dihalo ketones to the symmetrically substituted 2,4-dihalo isomers. In that connection, it is pertinent to mention that the only 2,2-dihalo-3-keto allo steroid which fails to undergo this rearrangement is the 2,2-dichloro derivative (I) and inspection of models clearly demonstrates that the hindrance between an axial chlorine atom at C-2 and the angular methyl group is very much smaller than that of an axial bromine atom and this latter case thus may not require a boat conformation of ring A.

Two possible explanations may be offered for the formation of the same 2β-bromo-2α-chloro ketone VII in both reactions (from II and III). It has been pointed out recently (16) that halogenation of a ketosteroid invariably first leads to that epimer in which the halogen atom is axially-oriented and that subsequent equilibration may or may not occur under thermodynamically controlled conditions (as do prevail in our halogenations). Based on this argument, the bromination of 2α-chlorocholestanone (II) to VII is unexceptional since the bromine atom in the final product (VII) is axial. On the other hand, the initial product in the chlorination of 2α-bromocholestanone (III) should be the 2α-bromo-2β-chloro isomer and equilibration to VII must then have occurred subsequently, possibly by reduction to BrCl in the presence of the excess hydrogen chloride and rebromination to VII. An alternate explanation[4] is that 2α-bromocholestanone (III) undergoes rapid halogen exchange with chlorine to 2α-chlorocholestanone (II) which is then brominated by BrCl to VII. Both explanations are based on the assumption that ring A is in the chair form (*vide supra*) and that the bromine atom is indeed axial.

In contrast to 2,2-dichlorocholestanone (I), the 2-chloro-2-bromo ketone VII

[4] Private communication from Dr. E. J. Corey, University of Illinois.

readily undergoes rearrangement in the presence of hydrogen bromide[5] to 2α-chloro-4α-bromocholestanone (VI). The di-equatorial orientation of the halogen atoms is indicated by the position of the infrared carbonyl band at 5.68 μ and the characteristic (3–5) levorotatory change after rearrangement. That the bromine rather than chlorine atom in VII had migrated (a further indication of the axial orientation of the former) was demonstrated as follows. Brief treatment of VI with collidine resulted in the formation of 0.97 equivalent of collidine hydrobromide and the isolation of an unsaturated monochlorocholestenone, which must be Δ^4-2α-chlorocholesten-3-one (X) since it exhibited an ultraviolet absorption maximum at 244 mμ, identical in position that that of Δ^4-2-bromocholesten-3-one (8) and furnished Δ^4-cholestenone (XV) on reduction with chromous chloride. The identical Δ^4-2-chlorocholesten-3-one (X) was produced in even better yield when 2α-chloro-4α-bromocholestanone (VI) was refluxed with sodium iodide in methyl ethyl ketone solution. This observation is of some theoretical significance since it has a bearing on the as yet somewhat obscure mechanism of the formation of a 2-iodo- Δ^4-3-ketosteroid by sodium iodide treatment (17) of a 2,4-dibromo-3-ketosteroid (IV). This is the key reaction in the conversion of a 3-keto allo steroid to the corresponding Δ^4-3-ketone [*e.g.* dihydroallocortisone acetate → cortisone acetate (18)] and since in that instance it was demonstrated (17) that the primary intermediate was a 2-iodo-4-bromo-3-ketone, the mechanistic possibility was left open that the dehydroiodination generating the 4,5-double bond was initiated by the 2-iodine atom acting as an internal base. The presently cited experiment (VI → X) removes the necessity for this assumption and leaves open for consideration either a thermal elimination of HI or the effect of iodide (present in excess in the reaction medium) acting as an "external" base.

Further confirmation for the Δ^4-2-chlorocholestenone (X) structure was adduced by the behavior of this substance upon treatment with 2,4-dinitrophenylhydrazine which completely paralleled that of Δ^4-2-bromocholestenone (8). In each instance there was observed a rearrangement with concomitant formation of the 2,4-dinitrophenylhydrazone of $\Delta^{4,6}$-cholestadien-3-one (XVI).

Independent proof for the structure and, in part, stereochemistry of 2α-chloro-4α-bromocholestanone (VI) was provided by a modification of the method first devised by Fieser and collaborators (19) for mono-bromo-3-keto steroids. The 2-chloro-4-bromo-3-ketone was reduced with sodium borohydride leading to 2α-chloro-4α-bromocholestan-3α-ol (XI) which upon catalytic debromination followed by acetylation furnished some of the known (1) 2α-chlorocholestan-3α-ol acetate (XII), thus confirming the 2α-configuration of the chlorine atom in the starting ketone (VI). It is interesting to note that while sodium borohydride reduction of cholestanone leads predominantly to cholestan-3β-ol (20),

[5] It is important to note that when the 2-chloro-2-bromo-3-ketone (VII) was treated with a large excess (smaller amounts were ineffective) of hydrogen chloride, the same 2-chloro-4-bromo-3-ketone (VI) was obtained, accompanied by some 2-chlorocholestanone (II). It would appear that in both instances (HBr and HCl catalyzed rearrangement), the initial step is reduction to Br_2 or BrCl followed by rebromination at C-4.

the introduction of two α-oriented, adjacent, bulky substituents results in a reversal of the stereochemical course of this reduction. On occasion, this may provide a satisfactory route to the relatively inaccessible 3α-alcohols of the 5 (allo) series and this is exemplified in the experimental section by conversion of 2α,4α-dibromocholestanone (IV) *via* the 3α-alcohol V to epicholestanol (IX).

In one experiment, 2α-chloro-4α-bromocholestan-3α-ol (XI) was treated with ethanolic sodium hydroxide. The only product, isolated in good yield, was an acid, which is formulated as XIII and which is believed to have arisen by initial dehydrohalogenation to a monohaloketone (2-chlorocholestanone?) followed by Favorskii rearrangement (*cf.* 21).

EXPERIMENTAL[6]

2,2-Dichlorocholestanone (I). To a solution of 2.95 g. of 2α-chlorocholestanone (II) (1) in 20 cc. of chloroform and 250 cc. of glacial acetic acid containing a trace of hydrogen chloride was added a solution of 0.99 g. of chlorine gas in 30 cc. of acetic acid. After standing at room temperature for 16 hrs., the reaction mixture was poured into much water and extracted with ether. The residue from the ether extraction was crystallized from ethanol-ether to furnish 2.47 g. of dichlorocholestanone with m.p. 144–147°. Further recrystallization from hexane yielded 1.87 g. of the analytical sample with m.p. 154–155°, undepressed upon admixture with the by-product from the *tert*-butyl hypochlorite chlorination of cholestanone (1), $[\alpha]_D^{22}$ +121°, $\lambda_{max.}^{CHCl_3}$ 5.78 μ.

Anal. Calc'd for $C_{27}H_{44}Cl_2O$: C, 71.18; H, 9.74.
Found: C, 71.23; H, 9.80.

The substance was recovered unchanged after standing overnight in acetic acid solution containing anhydrous hydrogen bromide.

Δ^1-*2-Chlorocholesten-3-one* (VIIIa). (*a*) *From 2,2-dichlorocholestanone* (I) *with collidine.* A solution of 300 mg. of the 2,2-dichloroketone (I) in 5 cc. of redistilled γ-collidine (Schweizerische Teerindustrie, A.G.) was refluxed for 20 min. in an atmosphere of nitrogen, producing 109 mg. (105%) of collidine hydrochloride. After processing the reaction mixture in the usual manner (3–5), the residue was chromatographed on 12 g. of alumina and the hexane-benzene (6:4) eluates were pooled and recrystallized from ethanol; yield, 64 mg., m.p. 115–117°, $[\alpha]_D^{23}$ +45°, $\lambda_{max.}^{EtOH}$ 246 mμ, log ϵ 3.99, $\lambda_{max.}^{CHCl_3}$ 5.95 μ.

Anal. Calc'd for $C_{27}H_{43}ClO$: C, 77.38; H, 10.34; Cl, 8.46.
Found: C, 77.09; H, 10.08; Cl, 8.27.

(*b*) *From 2-bromo-2-chlorocholestanone* (VII). Treatment of 300 mg. of VII with collidine exactly as described above yielded 120 mg. of VIIIa with m.p. 116–117°, not depressed when mixed with a specimen prepared according to (a); Found: C, 77.61; H, 10.57.

As further proof, 50 mg. of the 2-bromo-2-chloro ketone was treated with 22 mg. of 2,4-dinitrophenylhydrazine in glacial acetic acid in the standard manner and gave 49 mg. of the dinitrophenylhydrazone VIIIb with m.p. 270–273°, undepressed upon admixture with a sample described earlier (1); Found: C, 65.85; H, 8.24; N 9.35; Cl, 5.53.

(*c*) *By cleavage of* Δ^1-*2-chlorocholestenone 2,4-dinitrophenylhydrazone* (VIIIb). To a hot solution of 0.5 g. of 2,2-dichlorocholestanone in 10 cc. of acetic acid was added 250 mg. of dinitrophenylhydrazine. After refluxing for 5 min. in an atmosphere of nitrogen, the mixture was cooled, and the hydrazone was collected and then refluxed for 16 hrs. with 100 cc.

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[6] All melting points are uncorrected. Rotations were determined in chloroform solution. Infrared spectra were measured with a Baird double beam infrared spectrophotometer using sodium chloride cells of 0.1-mm. thickness. The microanalyses were performed by Geller Laboratories, Hackensack, New Jersey and by Miss Phyllis Tocco of Wayne University.

of chloroform, 150 cc. of acetone, and 5 cc. of hydrochloric acid.[3] At the end of this time there was added 7 g. of stannous chloride dissolved in 40 cc. of water and 25 cc. of hydrochloric acid and refluxing was continued for one hour. After removal of most of the acetone *in vacuo*, benzene was added and the organic layer was extracted with 10% hydrochloric acid until no more color was removed. The resulting residue was chromatographed on 35 g. of alumina and the hexane-benzene (1:1) eluates were recrystallized from ethanol to give 345 mg. of VIIIa with m.p. 116–117°, $[\alpha]_D^{22}$ +46°.

2-Chloroandrostane-3,17-dione. Androstane-3,17-dione (2.0 g.) in 20 cc. of glacial acetic acid was chlorinated with 0.87 g. (1.05 equiv.) of *tert*-butyl hypochlorite in the previously described manner (1) to yield 1.46 g. of 2-chloroandrostane-3,17-dione with m.p. 207–208° (after recrystallization from acetone-hexane), $[\alpha]_D^{23}$ +119°, $\lambda_{max.}^{CHCl_3}$ 5.78 μ. The same substance could be obtained in about 50% yield by the direct oxidation-chlorination of epiandrosterone with 2.1 equiv. of *tert*-butyl hypochlorite.

Anal. Calc'd for $C_{19}H_{27}ClO_2$: C, 70.68; H, 8.43; Cl, 10.98.
Found: C, 70.77; H, 8.59; Cl, 11.18.

2,2-Dichloroandrostane-3,17-dione. Employing the conditions described above for I, 1.9 g. of 2-chloroandrostane-3,17-dione was chlorinated with 0.5 g. of chlorine in acetic acid solution to give 1.07 g. of the 2,2-dichloro derivative with m.p. 199–201° (from ethanol-hexane), $[\alpha]_D^{21}$ +176°, $\lambda_{max.}^{CHCl_3}$ 5.77 μ.

Anal. Calc'd for $C_{19}H_{26}Cl_2O_2$: Cl, 19.85. Found: Cl, 19.99.

Reaction of 2-chlorocholestanone (II) *with lithium chloride.* A solution of 1.0 g. of II and 1.0 g. of lithium chloride in 30 cc. of redistilled dimethylformamide was refluxed for 5 hrs. and poured into 200 cc. of water. Ether extraction, chromatography of the oily residue on 50 g. of activated alumina, and elution with hexane-benzene (4:6) followed by recrystallization from methanol yielded 0.4 g. of Δ^1-*cholesten-3-one* (XIV) with m.p. 95–96°, undepressed upon admixture with an authentic sample, $\lambda_{max.}^{EtOH}$ 231 mμ, log ϵ 3.95.

Further elution of the chromatogram with hexane-benzene (3:7) furnished 0.285 g. of Δ^4-*cholesten-3-one* with m.p. 76–79°, $\lambda_{max.}^{EtOH}$ 242 mμ, log ϵ 4.24, identified by direct comparison with an authentic sample.

Essentially the same results were obtained when lithium bromide was substituted for lithium chloride.

2-Bromo-2-chlorocholestan-3-one (VII). (*a*) *By chlorination of 2-bromocholestanone* (III). A solution of 1.9 g. of 2α-bromocholestanone in 250 cc. of glacial acetic acid containing a small amount of hydrogen chloride was treated with 300 mg. of chlorine in 25 cc. of acetic acid for 12 hours. The bulk of the acetic acid was removed under reduced pressure and the product was extracted with ether and washed well with water. Evaporation and crystallization from ethanol-hexane led to 1.65 g. of crude material with m.p. 125–134°. Further recrystallization raised the m.p. to 145–147° (1.07 g.), $[\alpha]_D^{22}$ +117°, $\lambda_{max.}^{CHCl_3}$ 5.77 μ, $\nu_{max.}^{CCl_4}$ 1742 cm.$^{-1}$.[7]

Anal. Calc'd for $C_{27}H_{44}BrClO$: C, 64.85; H, 8.87; Cl, 7.09; Br, 15.98.
Found: C, 64.27; H, 9.05; Cl, 6.93; Br, 15.63.

(*b*) *By bromination of 2α-chlorocholestanone* (II). A solution of 2.57 g. of the chloro ketone II in 600 cc. of glacial acetic acid was treated with 1.03 g. of bromine in 16 cc. of the same solvent. The course of the bromination was followed by observing the change in optical rotation of an aliquot (*cf.* 4,5). As soon as the highest rotation value was obtained, the reaction was quenched by pouring into a large excess of water. The product was collected and recrystallized from ethanol-chloroform; yield, 1.96 g., m.p. 135–139°. Further recrystallization from the same solvent led to the analytical sample with m.p. 145–146°, $[\alpha]_D^{22}$ +112°, infrared spectrum identical with that of the sample prepared according to (*a*).

2α-Chloro-4α-bromocholestan-3-one (VI). (*a*) *By direct bromination of 2α-chlorocholestanone* (II). A solution of 5 g. of 2-chlorocholestanone in 450 cc. of warm acetic acid

[7] We are indebted to Dr. R. Norman Jones, National Research Council, Ottawa, for these accurate measurements.

containing a few drops of 4 *N* hydrogen bromine in acetic acid was treated dropwise with 2.0 g. of bromine dissolved in 30 cc. of acetic acid. After 36 hrs. at room temperature, the reaction mixture was diluted with water, and the product was filtered and recrystallized from ethanol-chloroform to give 3.72 g. of colorless crystals with m.p. 195–196° (dec.), $[\alpha]_D^{21}$ +5°, $\nu_{max.}^{CCl_4}$ 1758 cm.$^{-1}$.[7]

Anal. Calc'd for $C_{27}H_{44}BrClO$: Br, 15.98; Cl, 7.09.

Found: Br, 15.68; Cl, 6.96.

(*b*) *By rearrangement of 2-bromo-2-chlorocholestanone* (VII) *with hydrogen bromide.*[7] A sample (230 mg.) of the *gem*-dihalo ketone VII in 35 cc. of acetic acid containing 1 cc. of 4 *N* hydrogen bromide in acetic acid was allowed to stand at room temperature for 24 hours. The reaction mixture was diluted with water, and the product was filtered and recrystallized from chloroformethanol; yield, 105 mg., m.p. 194–196° (dec.) undepressed upon admixture with a sample prepared according to (*a*).

While 2-chlorocholestanone is recovered unchanged (I) to the extent of 50% when treated with chromous chloride, this was not the case with the 2-chloro-4-bromo derivative VI; 1 g. treated with 40 cc. of chromous chloride solution (17) for 30 min. at room temperature gave 91% of cholestanone, identified by mixture melting point of the ketone and its dinitrophenylhydrazone with authentic samples.

(*c*) *By rearrangement of 2-bromo-2-chlorocholestanone* (VII) *with hydrogen chloride.* To a warm solution of 0.5 g. of VII in 70 cc. of glacial acetic acid was added 10 cc. of a saturated solution of hydrogen chloride in acetic acid. After 16 hrs. at room temperature, 300 cc. of water was added, and the product was collected and fractionally recrystallized from ethanol-ether. From the less soluble fraction, there was obtained 0.08 g. of 2-chlorocholestanone (II) while *ca.* 0.05 g. of the 2-chloro-4-bromo-3-ketone (VII) was isolated from the more soluble fractions. The remainder of the material was not amenable to effective separation.

2-Chloro-4-bromoandrostane-3,17-dione. The bromination of 3.93 g. of 2-chloroandrostane-3,17-dione was carried out exactly as described above for II and after recrystallization from chloroform-ethanol yielded 2.35 g. of colorless crystals with m.p. 198–199° (dec.), $[\alpha]_D^{20}$ +58°, $\lambda_{max.}^{CHCl_3}$ 5.78 μ.

Anal. Calc'd for $C_{19}H_{26}BrClO_2$: C, 56.80; H, 6.52; Br, 19.89; Cl, 8.83.

Found: 56.56; H, 6.49; Br, 20.01; Cl, 9.01.

Δ^4-*2-Chlorocholesten-3-one* (X). (*a*) *With collidine.* The 2-chloro-4-bromo ketone VI (1.0 g.) was refluxed for 10 min. with 20 cc. of collidine yielding 0.39 g. (97%) of collidine hydrobromide. After processing in the usual manner, the brown oil was chromatographed on 40 g. of alumina; elution with hexane-benzene (6:4) gave 0.42 g. of material which on recrystallization from ethanol produced 0.3 g. of colorless crystals with m.p. 94–96°, $[\alpha]_D^{20}$ +76°, $\lambda_{max.}^{EtOH}$ 244 mμ, log ϵ 4.03, $\lambda_{max.}^{CHCl_3}$ 5.95 μ.

Anal. Calc'd for $C_{27}H_{43}ClO$: C, 77.38; H, 10.34; Cl. 8.46.

Found: C, 77.02; H, 10.39; Cl, 8.51.

(*b*) *With sodium iodide.* A solution of 1.0 g. of the bromo-chloro ketone VI in 40 cc. of methyl ethyl ketone was refluxed for 10 hours in an atmosphere of nitrogen with 1 g. of sodium iodide and filtered; yield of sodium bromide, 0.2 g. The color was discharged by the addition of sodium thiosulfate solution and after dilution with water, the product was extracted with ether. Evaporation of the ether left 0.77 g. of an oil ($\lambda_{max.}^{EtOH}$ 243 mμ) which on crystallization from methanol yielded 0.39 g. of colorless crystals with m.p. 95–96°, undepressed on admixture with a specimen prepared according to (*a*).

A solution of 0.1 g. of the unsaturated chloro ketone (X) in 75 cc. of acetone was treated with 10 cc. of chromous chloride solution (17) for 30 min. in an atmosphere of CO_2. After processing in the usual manner there was isolated 51 mg. of Δ^4-cholestenone (XV) with m.p. 80–81°. Identity was confirmed by mixture melting point and infrared comparison.

Reaction of Δ^4-*2-chlorocholestenone* (X) *with 2,4-dinitrophenylhydrazine.* A sample (75 mg.) of the unsaturated chloroketone X was heated in acetic acid solution with 50 mg. of dinitrophenylhydrazine for 5 min. One recrystallization of the crude product from ethanol-chloro-

form produced 43 mg. of dark-red crystals of the *dinitrophenylhydrazone of* $\Delta^{4,6}$*-cholestadien-3-one* (XVI) with m.p. 220–223°, undepressed upon admixture with an authentic sample (8), typical (6) u.v. maxima ($CHCl_3$) at 310 and 402 mμ, log ε 4.1 and 4.5.

2α,4α-Dibromocholestan-3α-ol (V). A suspension of 1.0 g. of 2,4-dibromocholestanone in 50 cc. of ethanol was stirred at room temperature for 12 hrs. with 0.4 g. of sodium borohydride. Dilution with water, filtration, and chromatography of the crude precipitate on 60 g. of alumina furnished 0.11 g. of material (4:6 hexane-benzene eluates) with m.p. 119–120° which was not further investigated and from the benzene-ether (8:2) eluates 0.64 g. of colorless crystals with m.p. 179–180°, $[\alpha]_D^{20}$ −12°, which gave no precipitate with alcoholic digitonin solution.

Anal. Calc'd for $C_{27}H_{46}Br_2O$: C, 59.34; H, 8.49.
Found: C, 59.55; H, 8.56.

The above dibromo alcohol V (200 mg.) in 20 cc. of ethanol containing 20 mg. of potassium hydroxide was hydrogenated with 0.5 g. of 5% palladized charcoal catalyst for 3 hrs. Filtration of the catalyst, dilution with water, extraction of the product with ether, and finally recrystallization from methanol-ether afforded 82% of epicholestanol (IXa) with m.p. 179–181° and upon acetylation, the acetate IXb with m.p. 94–96°. Both products were identified by mixture melting point comparisons with authentic samples.

2α-Chloro-4α-bromocholestan-3α-ol (XIa). The reduction of 6.68 g. of the chloro-bromo ketone VI was carried out with 1.0 g. of sodium borohydride in 350 cc. of ethanol exactly as described above. Careful chromatography on 200 g. of alumina and elution with benzene-ether (9:0) gave 29 homogenous fractions with m.p. 168–170°. Recrystallization from methanol-ether yielded 4.2 g. of the pure alcohol with m.p. 170–172°, $[\alpha]_D^{21}$ −15°, no precipitate with digitonin.

Anal. Calc'd for $C_{27}H_{46}BrClO$: C, 64.59; H, 9.24.
Found: C, 64.53; H, 9.47.

The *acetate* XIb was produced in 92% yield, m.p. 173–174°.

Anal. Calc'd for $C_{29}H_{48}BrClO_2$: C, 64.02; H, 8.89.
Found: C, 63.84; H, 8.83.

Hydrogenation of 350 mg. of the alcohol XIa under the conditions employed for the dibromo alcohol V followed by crystallization from methanol-ether produced 70 mg. of recovered starting material and from the filtrate 105 mg. of material with m.p. 100–104°. This was acetylated directly with pyridine-acetic anhydride and after crystallization from methanol ether yielded 45 mg. of 2α-chlorocholestan-3α-ol acetate with m.p. 190–193°, undepressed on admixture with an authentic specimen (1).

In one experiment devised to test the stability of 2α-chloro-4α-bromocholestan-3α-ol (XIa) towards base, 0.23 g. of the alcohol was refluxed for 12 hrs. with 0.5 g. of potassium hydroxide and 20 cc. of ethanol. Dilution with water gave a clear solution which afforded a colorless precipitate (0.185 g.) after acidification. Recrystallization from methanol-ether gave 0.15 g. of a halogen-free acid (*presumably XIII*) with m.p. 123–125°.

Anal. Calc'd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52.
Found: C, 80.08; H, 11.89.

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SUMMARY

2,2-Dichlorocholestanone (I) can be dehydrochlorinated with collidine or 2,4-dinitrophenylhydrazine to Δ^1-2-chlorocholesten-3-one (VIII) but it cannot be rearranged with hydrogen bromide to a 2,4-isomer. Chlorination of 2α-bromocholestanone (III) or bromination of 2α-chlorocholestanone (II) leads to

the same 2-bromo-2-chlorocholestanone (VII). Dehydrohalogenation furnishes Δ^1-2-chlorocholestenone while treatment with hydrogen bromide results in rearrangement to the 2α-chloro-4α-bromo isomer VI. The latter can be selectively dehydrobrominated with either collidine or sodium iodide to Δ^4-2-chlorocholestenone (X). Sodium borohydride reduction of either 2α-chloro-4α-bromo- or 2α,4α-dibromo-cholestanone furnishes predominantly the 3α-alcohol. Treatment of 2-chlorocholestanone with lithium chloride in dimethyl formamide solution results in the formation of a mixture of Δ^1- and Δ^4-cholestenone.

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