the fumarase active site. A comparison of these thermodynamic parameters with those for reactions of low molecular weight compounds should provide further information on the nature of the binding to the active site.

Acknowledgments.—We wish to thank Selma Hayman for the crystalline fumarase, Mark Takahashi for performing some of the experiments with D-tartrate and Eleanor Wigler for calculations of the experimental data.

[JOINT CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF STANFORD UNIVERSITY, STANFORD, CALIF., AND THE UNIVERSITY OF SOUTHAMPTON, SOUTHAMPTON, ENG.]

Optical Rotatory Dispersion Studies. XXXVI.[1] α-Haloketones (Part 7).[2] Demonstration of Boat Form in the Bromination of 2α-Methylcholestan-3-one[3,4]

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Kinetically controlled bromination of the enol acetate of 2α-methylcholestan-3-one yields 2α-bromo-2β-methylcholestan-3-one (V) in which ring A exists in the boat conformation (XIV). This conclusion, first uncovered by rotatory dispersion measurements, was confirmed by hydrogen bromide-promoted equilibration which led to the thermodynamically more stable 2β-bromo-2α-methylcholestan-3-one (VI) accompanied by the rearrangement product 2α-methyl-4α-bromocholestan-3-one (VII). Bromination of the enol acetate of cholestan-3-one affords directly 2α-bromocholestan-3-one under conditions where 2β-bromocholestan-3-one is stable. These results appear to be inconsistent with Corey's generalizations on the stereochemical course of ketone bromination.

Kinetically controlled bromination in the presence of pyridine[5] of the enol acetate IV of 2α-methylcholestan-3-one (III) affords[6] a monobromo derivative, which can also be obtained[6] by direct bromination of 2α-methylcholestan-3-one (III) itself. The location of the bromine atom at C-2 was established[6] by dehydrobromination to 2-methyl-Δ[1]-cholesten-3-one (VIII) and since infrared[7] and ultraviolet[8] measurements[9] indicated an axial orientation for the bromine atom, the product was assigned[6] the 2β-bromo-2α-methylcholestan-3-one (VI = XV) structure. Such an assumption seemed reasonable on the basis of Corey's generalization[10] that kinetically controlled bromination of a cyclohexanone always affords the axially oriented bromo ketone.

According to the axial haloketone rule[11,12] it would be predicted that a steroidal 2β-bromo-2α-methyl-3-ketone of the 5α-series (*e.g.*, VI) should exhibit a rotatory dispersion curve characterized by a strongly positive Cotton effect. Through the courtesy of Drs. Y. Mazur and F. Sondheimer,[6] a sample of their presumed 2β-bromo-2α-methylcholestan-3-one (VI) was obtained and its rotatory dispersion curve measured. In contrast to the anticipated strongly positive Cotton effect curve, a negative one was observed (see Fig. 1 in ref. 4) and this unexpected rotatory dispersion behavior prompted the presently recorded[4] re-examination of the bromination of 2α-methylcholestan-3-one (III). The results embodied in this article and the two succeeding ones[13,14] demonstrate that the stereochemical course of such brominations is considerably more complicated than envisaged originally[10] and that some modification is required in the currently accepted stereochemical picture[10] of the halogenation of cyclohexanones.

In our hands, the earlier reported[6] synthesis of 2α-methylcholestan-3-one (III) was not as convenient as the hydrogenolysis[15] of 2-hydroxymethylenecholestan-3-one (II). The formation of the enol acetate IV and its kinetically controlled[16] bromination were carried out as described earlier[6] and we were able to confirm the axial orientation of the bromine atom by infrared and ultraviolet spectral measurements (see Experimental). As noted above, the bromo ketone exhibited a negative Cotton effect (Fig. 1 in ref. 4), which according to the axial haloketone rule[11,12] is incompatible with the proposed[6] 2β-bromo-2α-methyl-3-ketone formulation VI. Nevertheless, the rotatory disper-

(1) Paper XXXV, J. Fishman and C. Djerassi, *Experientia*, **16**, 138 (1960).

(2) Part 6, C. Djerassi, E. J. Warawa, R. E. Wolff and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 917 (1960).

(3) Part of the experimental work was performed in the Departments of Chemistry of Wayne State University (Detroit, Mich.) and of Birkbeck College (London). Carl Djerassi and Neville Finch are indebted to the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, for financial assistance (grants CY-2919 and CY-4818).

(4) For preliminary communication see C. Djerassi, N. Finch and R. Mauli, THIS JOURNAL, **81**, 4997 (1959).

(5) E. R. H. Jones and D. J. Wluka, *J. Chem. Soc.*, 911 (1959).

(6) Y. Mazur and F. Sondheimer, THIS JOURNAL, **80**, 5220 (1958).

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

(8) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(9) The ultraviolet spectral properties are recorded in the Experimental section of the present paper.

(10) (a) E. J. Corey, *Experientia*, **9**, 329 (1953); (b) THIS JOURNAL, **76**, 175 (1954). A critical discussion of this paper will be found in ref. 14.

(11) (a) C. Djerassi and W. Klyne, *ibid.*, **79**, 1506 (1957); (b) C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958).

(12) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter 9.

(13) R. Mauli, H. J. Ringold and C. Djerassi, THIS JOURNAL, **82**, 5494 (1960).

(14) R. Villotti, H. J. Ringold and C. Djerassi, *ibid.*, **82**, Nov. 5 (1960).

(15) For pertinent references see Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, *ibid.*, **75**, 2567 (1953); M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956); H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, THIS JOURNAL, **81**, 427 (1959).

(16) The experimental conditions used by Mazur and Sondheimer (ref. 6) in the bromination of 2α-methylcholestan-3-one (III) itself (in contrast to those employed for its enol acetate IV) do not necessarily imply kinetic control since no particular precaution was taken to remove the hydrogen bromide formed in the bromination of the ketone. However, we have shown in the accompanying two papers (ref. 13, 14) that kinetically controlled bromination of a 2α-methyl-3-keto-5α steroid or its enol acetate leads to similar products.

sion curve also confirmed the axial orientation of the halogen atom, since its first rotatory dispersion extremum (trough[4] at 340 mμ) occurred at a considerably higher wave length than that (peak[17] at 310 mμ) of the halogen-free 2α-methylcholestan-3-one (III)—a typical bathochromic shift usually associated[8,11b,12] with the introduction of an axial bromine atom. Since the rotatory dispersion evidence is not consistent with a 2β-bromo-2α-methyl structure (VI = XV) nor does it permit the isomeric 2α-bromo-2β-methyl formulation in which ring A exists in the chair form (XIII)—an alternative which is also excluded by the infrared and ultraviolet spectral data—there remains for consideration only the boat form XIV of 2α-bromo-2β-methylcholestan-3-one. This represents an interesting instance where ultraviolet and infrared[18] measurements are unable to differentiate between structures XIV and XV, while this is a simple matter by means of optical rotatory dispersion. The axial haloketone rule[11,12] predicts a negative Cotton effect curve for 2α-bromo-2β-methylcholestan-3-one in the boat form XIV and since the 2α-bromine atom in this conformation is axially oriented, this structure is also in agreement with the observed spectral data. It has already been noted occasionally in the literature among polycyclic steroids and terpenes that a terminal[19] and even a nonterminal[20] ring may undergo a conformational change from a chair to a boat form if the proper driving force is present. This condition appears to be met in this instance, since in the chair form XIII of 2α-bromo-2β-methylcholestan-3-one (V), there is present an unfavorable diaxial methyl–methyl interaction as well as the unfavorable electrostatic situation[7,21] inherent in an equatorial α-bromocyclohexanone. Neither one of these two energetically detrimental factors is present in the boat conformation XIV; furthermore, the steric interaction between substituents in the 1- and 4-positions of a cyclohexane boat form is minimized in this case, because of the trigonal carbon atom bearing the carbonyl group.

So far, the new structure assignment XIV for the kinetic bromination product rests on rotatory dispersion evidence, on conformational considerations and finally on the dehydrobromination[6] of the bromo ketone to VIII, which we have confirmed by the lithium bromide–lithium carbonate–DMF procedure[22] as well as by the 2,4-dinitrophenylhydrazine method.[23] Independent proof has now been adduced while examining the question of whether the kinetically controlled product is also the thermodynamically preferred one. For this purpose, a chloroform–acetic acid solution of 2α-bromo-2β-methylcholestan-3-one (V = XIV) was allowed to stand overnight in the presence of hydrogen bromide. In contrast to the crystalline starting material V, the resulting crude product was oily, although analysis still indicated the presence of one bromine atom. Dehydrobromination of this mixture, under conditions[22] where the starting bromo ketone V afforded only 2-methyl-Δ¹-cholesten-3-one (VIII), now produced a chromatographically separable mixture of VIII and its double bond isomer, 2α-methyl-Δ⁴-cholesten-3-one (IX). This indicated that some bromine migration had occurred during the hydrogen bromide treatment and when the crude equilibration mixture was subjected to careful chromatography on silica gel, there could be isolated two new bromo ketones. The initially eluted product was shown to be 2β-bromo-2α-methylcholestan-3-one (VI = XV) on the following grounds: (a) the bromine atom had to be at C-2 because dehydrobromination[22,23] afforded 2-methyl-Δ¹-cholesten-3-one, uncontaminated by the Δ⁴-isomer IX; (b) the bromine atom possessed the axial orientation as demonstrated by the infrared[7] and ultraviolet[8] spectral properties of the substance; (c) its optical rotatory dispersion curve (Fig. 1 in ref. 4) was characterized by a powerful positive Cotton effect, which would be predicted for structure XV by the axial haloketone rule.[11,12] The isolation and structure proof of the 2β-bromo-2α-methyl-3-ketone VI represents rigorous proof for the correctness of our formulation XIV for the kinetically controlled bromination product, since otherwise it would be impossible to have two isomeric 2-bromo-2-methylcholestan-3-ones, each of them possessing an axially oriented bromine atom.

Further elution led to 2α-methyl-4α-bromocholestan-3-one (VII), since dehydrobromination[22] gave 2α-methyl-Δ⁴-cholesten-3-one (IX); the equatorial orientation of the bromine atom was established by infrared,[7] ultraviolet[8] and optical rotatory dispersion[11,12] (see Fig. 1 in ref. 4) measurements.

The above experimental results lead to the conclusion—rather unexpected in the light of Corey's generalizations[14,21]—that the kinetically controlled bromination product is the 2α-bromo-2β-methyl-3-ketone XIV with ring A in the boat form, while the thermodynamically preferred one is the 2β-bromo-2α-methyl-3-ketone XV with unchanged chair conformation in ring A. It is interesting to note that the boat form XIV is energetically preferred over its chair form XIII, but that the chair conformation XV is favored over either one of these. The energy differences[24] involved must be of a fairly small order of magnitude and as shown in one of the accompanying articles,[14] the chief role is clearly played by the angular methyl group, since the situation is completely altered upon its removal.

The question may be raised whether formation of the bromo ketone V in the boat form XIV under conditions of kinetic control is due to axial bromination of an intermediate possessing a boat confor-

(17) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, THIS JOURNAL, **80**, 4001 (1958).

(18) R. N. Jones (*ibid.*, **75**, 4839 (1953)) has already called attention to the fact that it is impossible to distinguish by the shift of the infrared carbonyl band between 2α-bromocholestan-3-one (XII) in the chair form and 2β-bromocholestan-3-one (X) in the boat conformation. An analogous situation obtains with XIV and XV.

(19) D. H. R. Barton, D. A. Lewis and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957); J. C. Banerji, D. H. R. Barton and R. C. Cookson, *ibid.*, 5041 (1957); N. L. Wendler, *Chemistry & Industry*, 1662 (1958).

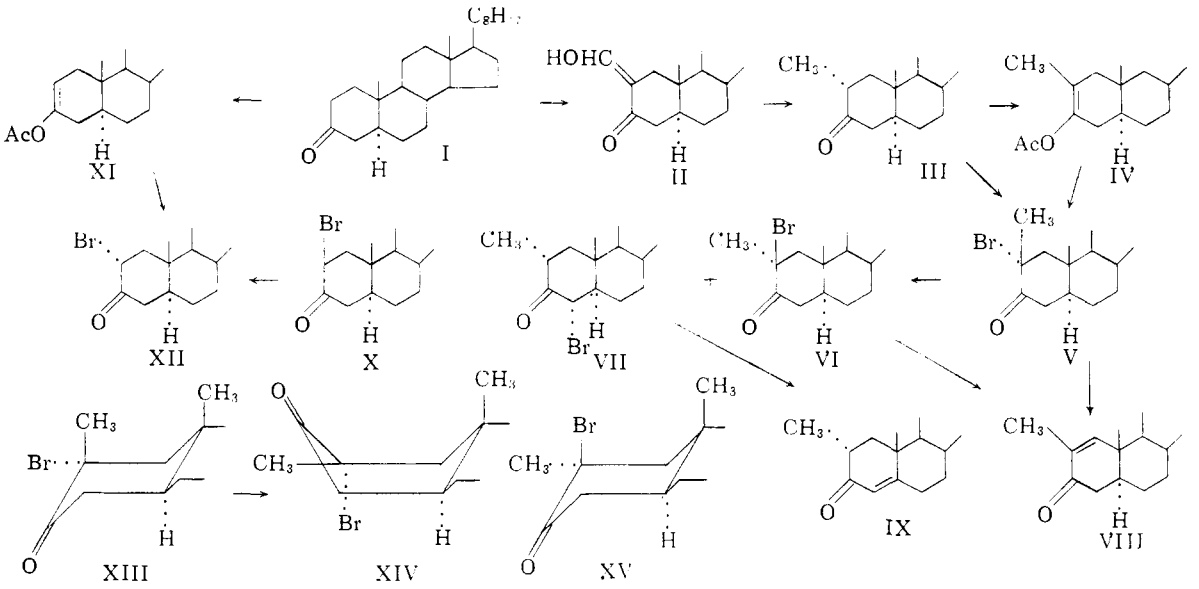
(20) C. Djerassi and J. S. Mills, THIS JOURNAL, **80**, 1236 (1958).

(21) E. J. Corey, *ibid.*, **75**, 2301 (1953), and later papers.

(22) R. Joly and J. Warnant, *Bull. soc. chim. France*, 367 (1958).

(23) V. R. Mattox and E. C. Kendall, THIS JOURNAL, **70**, 882 (1948); C. Djerassi, *ibid.*, **71**, 1003 (1949).

(24) It should be noted that the unfavorable energy difference between chair and boat forms of cyclohexanes is reduced by about 50% in the corresponding cyclohexanone (see N. L. Allinger, *ibid.*, **81**, 5727 (1959)).



mation—in which case our experimental results would still be consistent with the view[10,21] that kinetic control *always*[10a] involves axial attack—or due to equatorial approach of bromine in an intermediate of chair-like conformation. In either event rearward approach of bromine is required rather than the implied[10] topside entry which leads[6] to the incorrect structure VI. For reasons listed in detail in one[14] of the succeeding papers, we tend to favor the alternative involving a chair-like intermediate, which implies that the initially formed ketone is the equatorial 2α-bromo-2β-methyl-3-ketone V with a chair form (XIII) of ring A and that the latter then undergoes a conformational "flip" to the boat form XIV in order to minimize the above-mentioned unfavorable steric and electrostatic factors in XIII.

A pertinent experiment bearing on this last mechanistic point is the following. It has been predicted[10] that kinetically controlled bromination of cholestan-3-one (I) should give 2β-bromocholestan-3-one (X), which was unknown at the time that this statement was made. The substance has recently been prepared by an unambiguous route[25] and we have now found that 2β-bromocholestan-3-one (X) is readily isomerized to the equatorial isomer, 2α-bromocholestan-3-one (XII), under the conditions (acetic acid containing some hydrogen bromide) prevailing in the direct bromination of cholestan-3-one (I).[26] These are conditions favoring the formation of the thermodynamically preferred isomer and it is not surprising, therefore, that standard acid-catalyzed bromination[26] of cholestan-3-one (I) leads directly to 2α-bromocholestan-3-one (XII).[27] These results, though consistent with the view[10] that the initially formed (kinetic) product is 2β-bromocholestan-3-one (X) which then rearranges to XII, certainly do not prove it. The availability of the hypothetical intermediate X made it possible to devise conditions under which equilibration did not occur. Unfortunately, under those conditions (carbon tetrachloride–acetic acid–sodium acetate) cholestan-3-one (I) did not take up any appreciable amount of bromine. However, its enol acetate XI[28] readily reacted with bromine in the presence of sodium acetate to afford directly 2α-bromocholestan-3-one (XII), which by infrared examination could not have contained more than 5% of 2β-bromocholestan-3-one (X). This experiment proves that kinetically controlled bromination of the enol acetate XI gives directly the equatorial bromo ketone XII and thus supports our contention that this also applies to the enol acetate IV. If we assumed that the stereochemical course of the bromination of enol acetates and of ketones is substantially identical,[29] then it is necessary to modify Corey's views[10,21] with respect to the stereochemistry of kinetically controlled halogenation of cyclohexanones. These modifications and experimental justifications for them are cited in an accompanying article.[14]

Incidental to the above studies, alternate avenues to the structure proof of the bromination products of 2α-methylcholestan-3-one (III) were

(25) (a) C. W. Bird, J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 4149 (1957); (b) I. Malunowicz, J. Fajkos and F. Sorm, *Chem. Listy*, **52**, 2359 (1958).

(26) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935). For further references see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 8.

(27) L. F. Fieser and X. A. Dominguez, THIS JOURNAL, **75**, 1704 (1953); E. J. Corey, *ibid.*, **75**, 4832 (1953); L. F. Fieser and W. Y. Huang, *ibid.*, **75**, 4837 (1953).

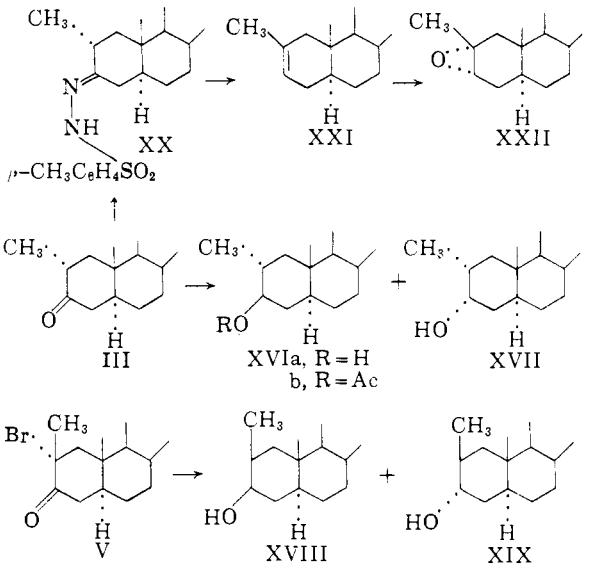
(28) W. G. Dauben, R. A. Micheli and J. F. Eastham, *ibid.*, **74**, 3852 (1952); M. Rubin and B. H. Armbrecht, *ibid.*, **75**, 3513 (1953).

(29) Jones and Wluka (ref. 5) have also noted that kinetically-controlled bromination of the enol acetate of 3β-acetoxycholestan-7-one affords substantial quantities of the equatorial 6α-bromo derivative. They did not challenge the validity of Corey's generalization (ref. 10) but rather assumed that a separate mechanism operates in the bromination of enol acetates, which proceeds through a cyclic transition state and thus always leads to the equatorial bromo ketone. We have been able to show with certain 19-nor steroids (ref. 14) that this is not the case and that such kinetically controlled bromination of enol acetates can give directly the axial bromo ketone *provided there are no opposing steric factors*. These detrimental steric factors (angular methyl group at C-10) are, however, present in 7-keto steroids, and we believe that the example of Jones and Wluka is simply another case of direct bottom side (equatorial) attack similar to the bromination of XI, without requiring a special mechanism.

undertaken. While these did not afford the desired information, they are nevertheless of sufficient intrinsic interest to merit brief mention.

The classical procedure[27] for proving chemically the stereochemistry of a steroidal α-bromo ketone has been the sodium borohydride or lithium aluminum hydride reduction to the bromohydrin followed by base treatment to an epoxide or ketone. By assuming *trans* elimination of the elements of hydrogen bromide and knowing the configuration of the alcoholic function in the bromohydrin, it is a simple matter to arrive at the orientation of the bromine atom. At the time that this reaction was studied by us with 2α-bromo-2β-methylcholestan-3-one (V), only one case had been described in the literature[30] where such a reduction had been attempted with a steroidal tertiary α-bromo ketone, and this resulted in loss of the halogen atom at the hydride reduction stage. Subsequently, several other examples of partial or complete loss of bromine under these conditions have been recorded[5,31] and it is not surprising, therefore, that similar loss of bromine was also encountered when the bromo ketone V was subjected to reduction with sodium borohydride. Nevertheless it is interesting to note that the mixture of alcohols resulting from this reaction consisted of 2β-methylcholestan-3β-ol (XVIII) and 2β-methylcholestan-3α-ol (XIX), rather than the corresponding 2α-methyl isomers XVI and XVII, which were isolated when the identical reduction was performed with 2α-methylcholestan-3-one (III).

A second approach, which was not studied in detail, involved 2α,3α-oxido-2β-methylcholestane (XXII). This required quantities of the previously unknown 2-methyl-Δ²-cholestene (XXI) and in this connection we examined the applicability of the Bamford–Stevens reaction[32] which has been studied only occasionally in the steroid series.[33] The base-catalyzed decomposition of the *p*-toluenesulfonyl hydrazone XX of 2α-methylcholestan-3-one proceeded smoothly and yielded the required 2-methyl-Δ²-cholestene (XXI). The position of the double bond was established by examination of its nuclear magnetic resonance spectrum and oxidation with perbenzoic acid afforded a homogeneous epoxide, to which structure XXII has been assigned by analogy to the peracid oxidation of Δ²-cholestene.[34] In contrast to the smooth hydrogen bromide opening of 2α,3α-oxidocholestane to 2β-bromocholestan-3α-ol,[35] a similar reaction of 2α,3α-oxido-2β-methylcholestane (XXII) gave a complicated mixture from which only one crystalline component could be separated. This proved to be 2α-methylcholestan-3-one (III) and it is conceivable that the ketone was produced by a direct shift of hydrogen[36] rather than through an intermediate bromohydrin.



Experimental[37]

2α-Methylcholestan-3-one (III).—Cholestan-3-one (I) (82 g.) was dissolved in sodium-dried thiophene-free benzene (1 l.) and added over a period of 1 hr. to a stirred suspension of 15 g. of freshly prepared sodium methoxide in 800 cc. of dry benzene containing 110 cc. of ethyl formate (dried over potassium carbonate and distilled). After adding an additional 5.0 g. of sodium methoxide and stirring for 4 hr., the reaction mixture was filtered and the collected solid was washed with benzene and dried overnight *in vacuo*. The bright yellow sodium salt of II was stirred for 1 hr. in a mixture of 85 cc. of concd. hydrochloric acid and 765 cc. of water, filtered and washed with water until the washings were neutral. The resulting pale yellow **2-hydroxymethylenecholestan-3-one** (II) (70 g., m.p. 164–166°) was used directly in the hydrogenation.

In view of the relative insolubility of II in ethanol or acetic acid, 4.54 g. of the 2-hydroxymethylene derivative II was dissolved in 50 cc. of warm thiophene-free benzene and added to a suspension of 2 g. of 10% palladized charcoal catalyst in 50 cc. of ethanol. The mixture was shaken in an atmosphere of hydrogen for 2 days, the catalyst removed, washed well with warm benzene and the combined washings and filtrate were taken to dryness under diminished pressure. The residue was chromatographed on 240 g. of alumina, elution with hexane removing 150 mg. of hydrocarbon (m.p. 96–97°, presumably 2-methylcholestane) which was not investigated further. Elution with benzene–hexane (6:4) provided 2.74 g. of crystals, which were recrystallized from ether–methanol to afford 2.25 g. of **2α-methylcholestan-3-one** (III),[6] m.p. 119.5–120°, $[\alpha]_D$ +44° (*c* 0.93), $\lambda_{max}^{CHCl_3}$ 5.84 μ, λ_{max}^{MeOH} 284 mμ (log ε 1.49).

The enol acetate IV[6] was prepared from 3.0 g. of III by the isopropenyl acetate method as described earlier[6] and, after chromatography on 180 g. of alumina, elution with hexane–benzene (8:2) afforded 2.8 g., m.p. 92–93°, $[\alpha]_D$ +67° (*c* 1.76), $\lambda_{max}^{CHCl_3}$ 5.74 and 8.06 μ.

Bromination of 2-Methyl-Δ²-cholesten-3-ol Acetate (IV).—A solution of 40 mg. of bromine in 1 cc. of acetic acid was added to 100 mg. of the enol acetate IV dissolved in 18 cc. of acetic acid and 2 cc. of pyridine.[5] After standing in the dark for 18 hr., the reaction mixture was poured into water,

(30) H. B. Henbest, E. R. H. Jones, A. A. Wagland and T. I. Wrigley, *J. Chem. Soc.*, 2477 (1955).

(31) E. R. H. Jones and D. J. Wluka, *ibid.*, 907 (1959); N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

(32) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959); L. Friedman and H. Shechter, THIS JOURNAL, **81**, 5512 (1959).

(33) See E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956); D. E. Evans and G. H. R. Summers, *J. Chem. Soc.*, 4821 (1956).

(34) A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

(35) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954).

(36) See R. C. Cookson and J. Hudec, *Proc. Chem. Soc.*, 24 (1957).

(37) Melting points were determined on the Kofler block. The infrared and ultraviolet spectral measurements were performed by Miss B. Bach, while the rotatory dispersion data are due to Mrs. T. Nakano. All microanalyses were carried out by Dr. A. Bernhardt, Mülheim, Germany. Unless noted otherwise all rotations were measured in chloroform solution. The alumina in all chromatograms was Merck "acid-washed."

extracted with ether and washed successively with 5% sodium bicarbonate, water, dilute hydrochloric acid and finally water. The dried ether extract was evaporated and the residue (107 mg.) was triturated with methanol. Recrystallization of the resulting solid from ether–methanol yielded 62 mg. of colorless needles of **2α-bromo-2β-methylcholestan-3-one** (V = XIV), m.p. 136–138°, $\lambda_{max}^{CHCl_3}$ 5.83 μ, $\lambda_{max}^{cyclohexane}$ 313 mμ (log ε 2.17); R.D. (Fig. 1 in ref. 4) in methanol (*c* 0.088): $[\alpha]_{700}$ −20°, $[\alpha]_{589}$ −30°, $[\alpha]_{340}$ −1180°, $[\alpha]_{292}$ +1960°, $[\alpha]_{260}$ +960°. This substance was shown to be identical by direct comparison with the supposed 2β-bromo-2α-methylcholestan-3-one of Mazur and Sondheimer,[6] to whom we are indebted for a specimen.

Dehydrobromination of 2α-Bromo-2β-methylcholestan-3-one (V). (a) **With Lithium Bromide–Lithium Carbonate.**[22]—2α-Bromo-2β-methylcholestan-3-one (V) (100 mg.) was dissolved in 5 cc. of purified dimethylformamide, lithium bromide (100 mg.) and lithium carbonate (100 mg.) were added and the mixture was stirred at 95° for 18 hr. It was then poured into 150 cc. of dilute sulfuric acid, extracted with ether, washed well with water, dried and evaporated The residual glass was chromatographed on 10 g. of alumina and **2-methyl-Δ¹-cholesten-3-one (VIII)**[6] was eluted with benzene–hexane (6:4); yield 75 mg., m.p. 75–76°, $\lambda_{max}^{CHCl_3}$ 6.00 μ, λ_{max}^{EtOH} 240 mμ (log ε 3.97).

(b) **With 2,4-Dinitrophenylhydrazine.**[23]—2α-Bromo-2β-methylcholestan-3-one (V) (150 mg.) was dissolved in hot glacial acetic acid in an atmosphere of nitrogen, 70 mg. of 2,4-dinitrophenylhydrazine was added and the mixture was boiled for 2 min. After cooling, the precipitated **2,4-dinitrophenylhydrazone** (102 mg.) of 2,-methyl-Δ¹-cholesten-3-one (VIII) was recrystallized from benzene–ethanol to afford 84 mg. of orange needles, m.p. 252–253°. The analytical sample exhibited m.p. 255–256°, $\lambda_{max}^{CHCl_3}$ 384 mμ (log ε 4.44).

Anal. Calcd. for $C_{34}H_{50}N_4O_4$: C, 70.55; H, 8.70; N, 9.65. Found: C, 70.35; H, 8.54; N, 9.72.

The identical 2,4-dinitrophenylhydrazone (32 mg., m.p. 254–255°) was obtained when 33 mg. of 2-methyl-Δ¹-cholesten-3-one (VIII) was treated with Brady reagent.

Equilibration of 2α-Bromo-2β-methylcholestan-3-one (V) with Hydrogen Bromide.—To a solution of 850 mg. of the bromo ketone V in 50 cc. of chloroform–acetic acid (1:1) was added 8 drops of 15% hydrogen bromide in acetic acid solution, the mixture was stirred in the dark at room temperature for 23 hr., poured into 10% potassium bicarbonate solution and ether extracted. The ether was washed with water, dried and removed *in vacuo* to leave 766 mg. of oily residue (*Anal.* Calcd. for $C_{28}H_{47}BrO$: Br, 16.62. Found: Br, 15.60). This material was chromatographed on 75 g. of silica gel, elution with hexane–benzene (7:3) yielding 239 mg. of semi-solid, which was crystallized from ether–methanol to afford 120 mg. of **2β-bromo-2α-methylcholestan-3-one** (VI), m.p. 115–121°. Further recrystallization provided 76 mg. of the analytical specimen, m.p. 120–122°, $\lambda_{max}^{CHCl_3}$ 5.84 μ, $\lambda_{max}^{dioxane}$ 308 mμ (log ε 2.06); R.D. (Fig. 1 in ref. 4) in dioxane (*c* 0.092): $[\alpha]_{700}$ +97°, $[\alpha]_{589}$ +140°, $[\alpha]_{335}$ +2920°, $[\alpha]_{285}$ −2960°, $[\alpha]_{272}$ −2400°.

Anal. Calcd. for $C_{28}H_{47}BrO$: Br, 16.62. Found: Br, 17.01.

Further elution with hexane–benzene (6:4) provided 118 mg., which was crystallized from ether–methanol to give 61 mg. of **2α-methyl-4α-bromocholestan-3-one (VII)**, m.p. 136–138°. Further recrystallization raised the m.p. to 140–141°, $\lambda_{max}^{CHCl_3}$ 5.77 μ, $\lambda_{inflect}^{dioxane}$ 285 mμ (log ε 1.60); R.D. (Fig. 1 in ref 4) in dioxane (*c* 0.102): $[\alpha]_{700}$ −29°, $[\alpha]_{589}$ −27°, $[\alpha]_{305}$ + 300°, $[\alpha]_{280}$ −50°.

Anal. Calcd. for $C_{28}H_{47}BrO$: Br, 16.62. Found: Br, 16.19.

Continued elution of the column led to 190 mg. of 2-methyl-Δ¹-cholesten-3-one (VIII).

An attempt was made to perform the equilibration of 200 mg. of 2α-bromo-2β-methylcholestan-3-one in the presence of β-naphthol[38] in order to establish a hydrogen bromide-catalyzed debromination–rebromination mechanism for the equilibration. The crude neutral product (173 mg.) was indeed largely bromine-free (*Anal.* Calcd. for $C_{28}H_{47}BrO$: Br, 16.62. Found: Br, 5.80), but chromatography afforded only 12 mg. of pure 2α-methylcholestan-3-one (III). The phenolic fraction contained only a small amount of α-bromo-β-naphthol (*Anal.* Calcd. for $C_{10}H_7BrO$: Br, 35.9. Found: Br, 6.1), whose presence was indicated by paper chromatographic analysis in 6% acetic acid and spraying with diazotized *p*-nitroaniline.

Dehydrobromination of 2β-Bromo-2α-methylcholestan-3-one (VI).—The dehydrobromination of 18 mg. of the bromo ketone VI was performed in 2 cc. of dimethylformamide with lithium bromide–lithium carbonate[22] exactly as described for the isomer V and yielded 14 mg. of 2-methyl-Δ¹-cholesten-3-one (VIII), m.p. 69–72°. One recrystallization from methanol raised the m.p. to 72–74°, λ_{max}^{MeOH} 241 mμ (log ε 3.95), $\lambda_{max}^{CHCl_3}$ 5.99 μ. The absence of the characteristic 6.17 μ band[6] demonstrates that the product is uncontaminated by the Δ⁴-isomer IX.

Similarly, dehydrobromination of VI with 2,4-dinitrophenylhydrazine in acetic acid solution[32] provided **2-methyl-Δ¹-cholesten-3-one 2,4-dinitrophenylhydrazone**, m.p, p. 254–256°, whose identity with the above-described specimen was established by mixture melting point and infrared comparison.

Dehydrobromination of 2α-Methyl-4α-bromocholestan-3-one (VII).—When the above-described lithium bromide–lithium carbonate dehydrobromination[22] was performed with 18 mg. of 2α-methyl-4α-bromocholestan-3-one (VII), there was obtained 13 mg. of a clear oil, which crystallized on contact with methanol. One recrystallization from methanol afforded **2α-methyl-Δ⁴-cholesten-3-one (IX)**,[6,39] m.p. 120–122°, λ_{max}^{MeOH} 242 mμ (log ε 4.15), $\lambda_{max}^{CHCl_3}$ 5.99 and 6.17 μ.

Its 2,4-dinitrophenylhydrazone was recrystallized from benzene–ethanol; m.p. 224–226°, $\lambda_{max}^{CHCl_3}$ 385 mμ (log ε 4.45).

Anal. Calcd. for $C_{34}H_{50}N_4O_4$: C, 70.55; H, 8.70; N, 9.65. Found: C, 70.63; H, 8.59; N, 9.54.

Stability of 2β-Bromocholestan-3-one (X).—2β-Bromocholestan-3-one (X)[25] dissolved in acetic acid containing a trace of hydrogen bromide is isomerized at room temperature to 2α-bromocholestan-3-one (XII). However, when X was dissolved in a mixture of acetic acid–carbon tetrachloride containing sodium acetate (*vide infra*) and left at room temperature for 1 hr., polarimetric determination showed that at least 75% of 2β-bromocholestan-3-one (X) remained unchanged.

Bromination of Δ²-Cholesten-3-ol Acetate (XI).—The solvent used in this experiment was prepared by mixing 160 cc. of glacial acetic acid, 40 cc. of carbon tetrachloride and 2.0 g. of anhydrous sodium acetate. 3-Acetoxy-Δ²-cholestene (XI)[28] (m.p. 93–98°, $[\alpha]_D$ +60° (*c* 1.11)) was dissolved in 20 cc. of the above solvent and 2.4 cc. of bromine solution (0.75 cc. of bromine in 50 cc. of the solvent) was added dropwise with stirring over a period of 30 min. The reaction mixture was poured into excess water and extracted with methylene chloride. The extract was washed several times with water until the *p*H was 5.0. Then followed a sodium bicarbonate wash and finally three washes with distilled water. The methylene dichloride solution was dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo* at room temperature. The crude residue had $[\alpha]_D$ +64° (*c* 1.64) and its infrared spectrum[40] (carbon disulfide) indicated the presence of 90% of 2α-bromocholestan-3-one (XII), 5% of 2β-bromocholestan-3-one (X) and 5% of enol acetate XI. One recrystallization from ether–methanol gave 2α-bromocholestan-3-one (XII), m.p. 167–168°, $[\alpha]_D$ +40° (*c* 1.12).

Sodium Borohydride Reduction of 2α-Methylcholestan-3-one (III).—The lithium aluminum hydride reduction of III to 2α-methylcholestan-3β-ol (XVIa) has already been recorded,[6] but it was necessary to carry out this reduction with sodium borohydride for comparison with the course of a similar reduction of the bromo ketone V described below.

2α-Methylcholestan-3-one (III) (200 mg.) was dissolved in 50 cc. of methanol, a little ether being added to obtain complete solution at room temperature. An aqueous solution of 500 mg. of sodium borohydride was added followed by 1 cc. of saturated sodium carbonate. After standing at room temperature for 2 hr., the mixture was concentrated under diminished pressure, diluted with water and

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

(39) M. Mousseron, F. Winternitz and A. C. de Paulet, *Compt. rend.*, **245**, 1859 (1957); J. A. K. Quartey, *J. Chem. Soc.*, 1710 (1958).

(40) The specific bands in the infrared that were used in examining the crude bromination product were: **X** (5.81) and (10.58 μ), **XI** (5.70 and acetate bands in 8.1 μ region), **XII** (5.76 μ).

extracted with ether. Removal of the ether left a white solid (208 mg., m.p. 127–131°). A portion (109 mg.) was chromatographed on 11 g. of alumina. Elution with hexane–benzene (1:1) gave material (17 mg., m.p. 90–103°) which on two recrystallizations from aqueous ethanol provided 3 mg. of colorless solid, m.p. 99–103°, $\lambda_{max}^{CS_2}$ 2.80 and 10.21 μ. The substance did not give a precipitate with digitonin solution and is, therefore, assumed to be **2α-methylcholestan-3α-ol (XVII)**. From further fractions eluted by hexane–benzene (4:6) 86 mg. of crystals (m.p. 124–138°) was obtained, which on recrystallization from ethanol afforded 65 mg. of **2α-methylcholestan-3β-ol (XVIa)**,[6] m.p. 140–141°, $[\alpha]_D$ +12° (*c* 1.47), $\lambda_{max}^{CS_2}$ 2.91 and 9.63 μ. The substance gave a heavy precipitate with digitonin solution and its acetate **XVIb**[6] had m.p. 104.5–106°.

Sodium Borohydride Reduction of 2α-Bromo-2β-methylcholestan-3-one (V).—The sodium borohydride reduction of 200 mg. of the bromo ketone V was performed exactly as described above for 2α-methylcholestan-3-one (III) except that the reaction mixture was left standing for 14 hr. The crude, amorphous product (178 mg.) was essentially bromine-free (*Anal.* Found: Br, 0.40). A 153-mg. portion was chromatographed on 15 g. of alumina and all the material was eluted by hexane–benzene (7:3) and collected in ten fractions, which crystallized from ether–methanol. Fractions 1–4 were combined and recrystallized from the same solvent to yield 32 mg. of crystals, m.p. 122–128° $[\alpha]_D$ +34° (*c* 0.85), $\lambda_{max}^{CS_2}$ 2.89 and 9.74 μ. Since this material did not give a precipitate with a digitonin solution and was different (infrared spectrum) from XVII, it is assumed to be **2β-methylcholestan-3α-ol (XIX)**.

Anal. Calcd. for $C_{28}H_{50}O$: C, 83.47; H, 12.52. Found: C, 83.67: H, 12.34.

Fractions 7–10 from the chromatogram were similarly recrystallized from ether–ethanol and afforded 55 mg., m.p. 121–124°, $[\alpha]_D$ + 30° (*c* 0.91).[41] The substance gave a precipitate with digitonin solution, but its infrared spectrum was distinctly different from that of 2α-methylcholestan-3β-ol (XVIa). Furthermore, oxidation with chromium trioxide in acetone solution led to 2β-methylcholestan-3-one[6] (m.p. 85–92°, $[\alpha]_D$ +90° (*c* 0.2), $\lambda_{max}^{CHCl_3}$ 5.84 μ), thus demonstrating that this alcohol was **2β-methylcholestan-3β-ol (XVIII)**.

Anal. Calcd. for $C_{28}H_{50}O$: C, 83.47; H, 12.52. Found: C, 83.87; H, 12.28.

2-Methyl-Δ²-cholestene (XXI).—To a refluxing solution of 2.5 g. of 2α-methylcholestan-3-one (III) and 1.25 g. of *p*-toluenesulfonylhydrazine in 30 cc. of ethanol was added concd. sulfuric acid (4 drops). A precipitate appeared immediately, which was collected, washed well with water and dried; yield 2.58 g. Recrystallization from benzene–ethanol afforded 1.64 g. of the benzene solvate of **2α-methylcholestan-3-one *p*-toluenesulfonylhydrazone (XX)**, m.p. 210° dec.

Anal. Calcd. for $C_{35}H_{56}N_2O_2S \cdot C_6H_6$: C, 76.11; H, 9.66; N, 4.33; S, 4.95. Found: C, 75.49; H, 10.24; N, 4.36; S, 4.81.

A solution of 200 mg. of the hydrazone XX in 10 cc. of diethyl carbitol was added to 1 g. of sodium dissolved in 30 cc. of ethylene glycol. The mixture was heated under reflux for 18 hr. in an atmosphere of nitrogen, diluted with water and extracted with benzene. Removal of the benzene left 120 mg. of an oil which was chromatographed on alumina. Elution with hexane yielded a colorless solid (80 mg.) which was recrystallized from ethanol to give colorless needles (55 mg.), m.p. 96–97°. The analytical sample of **2-methyl-Δ²-cholestene (XXI)** showed m.p. 97–97.5°, $[\alpha]_D$ +75° (*c* 0.74). The nuclear magnetic resonance spectrum[42] in deuteriochloroform with tetramethylsilane as an internal standard exhibited a signal at 319 c.p.s. from a proton on a doubly bonded carbon. The area of this signal relative to the area of the signals from the rest of the protons in the molecule was approximately 1:53, which is fairly close to that (1:48) calculated for 2-methyl-Δ²-cholestene (XXI). A higher gain spectrum showed a minor signal just to the right of the 319 c.p.s. peak and this is probably due to a small amount of an isomer with a terminal methylene group.

Anal. Calcd. for $C_{28}H_{48}$: C, 87.42; H, 12.58. Found: C, 87.49; H, 12.63.

2α,3α-Oxido-2β-methylcholestane (XXII).—To an ice-cold solution of 71 mg. of 2-methyl-Δ²-cholestene (XXI) in chloroform was added 0.5 cc. of a 0.817 *N* solution of perbenzoic acid in chloroform. After standing at 4° for 24 hr., the peracid uptake corresponded to one molar equivalent and the product was isolated in the usual manner. Recrystallization from ethanol led to 59 mg. of colorless needles, m.p. 95–97.5°, while the analytical sample exhibited m.p. 98–98.5°, $[\alpha]_D$ +35° (*c* 0.94).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.92; H, 12.08. Found: C, 83.90; H, 12.13.

A 202-mg. sample of the above epoxide was dissolved in 3 cc. of chloroform and shaken for 7 min. with 1 cc. of 40% hydrobromic acid. The reaction mixture was poured into 10% aqueous sodium sulfite solution and extracted with chloroform. Removal of the chloroform gave an oil which was chromatographed carefully on silica gel, the only crystalline product being 76 mg. of 2α-methylcholestan-3-one (III) which was eluted with benzene–hexane (6:4).

(41) ADDED IN PROOF.—We have been informed by Dr. A. Nickon of Johns Hopkins University that this substance has been prepared in his laboratory by another procedure (A. Nickon and J. B. DiGiorgio, to be published) and that these constants were observed: m.p. 134–135°, $[\alpha]_D$ + 42°. Comparison of our specimen with Dr. Nickon's gave no mixture melting point depression (m.p. 122–130°) and their infrared spectra (CS_2 solution) were identical. The divergence in rotation would suggest that our product is contaminated by the 2α-isomer XVIa.

(42) Courtesy of Varian Associates, Palo Alto, Calif.