The experiment was again repeated except that 1.0 g. of sodium methoxide was added to the mixture instead of the sulfuric acid. The products and yields (average of four experiments) were: ethanol, 18.3 g.; ethyl orthoformate, 40.9 g.; ethyl cyanoacetate, 27.2 g.; ethyl ethoxymethylenecyanoacetate, 20.1 g.; residue, 14 g.

Reaction of Ethyl Orthoformate with Ethyl Oxalacetate.—A mixture of 65 g. (0.44 mole) of pure, freshly distilled ethyl orthoformate and 47 g. (0.25 mole) of ethyl oxalacetate was heated in an oil-bath at 140° under reflux for eight hours. The liquid was distilled under reduced pressure and collected in two fractions. The first fraction b.p. up to 90° (10 mm.) was collected in a cold trap, and the second was taken up to 200° (2 mm.). A higher boiling residue, 20 g., remained in the flask. The first fraction was distilled through a packed column to give the following: 0.5 g., b.p. 55–75°; 18 g., b.p. 75–80°, identified as ethanol; 0.5 g., b.p. 80–142°; and 35 g., b.p. 142–144° identified as ethyl orthoformate. The higher boiling fraction was again distilled through a Vigreux column and 14 g. of liquid, b.p. 95–100° (2 mm.), was obtained which was thought to be ethyl oxalacetate. Following this, 17 g. (29% yield) of ethyl ethoxymethyleneoxalacetate[1] was obtained, b.p. 150–155° (0.7 mm.). This was characterized by conversion to the copper salt, m.p. 230–231° (uncor.). The meltin point was unchanged when mixed with the copper salt prepared from an authentic sample of ethyl ethoxymethyleneoxalacetate.[1]

In a duplicate experiment 22.5 g. (0.12 mole) of ethyl oxalacetate and 22.5 g. (0.15 mole) of ethyl orthoformate were heated together at 140° for two hours. The yield of ethyl ethoxymethyleneoxalacetate was 9.5 g. (32.5%).

Ethyl Orthoformate and Diethyl Malonate.—A mixture of 0.5 mole of ethyl orthoformate and 0.5 mole of diethyl malonate was heated under reflux for eight hours. There was no evidence that any reaction took place. Reaction also failed to take place in similar experiments in which 1 g. of sulfuric acid or 1 g. of sodium methoxide was added to the mixture. In each case the starting materials were recovered almost quantitatively by fractional distillation.

When mixtures of 0.25 mole of diethyl ethoxymethylenemalonate and 1.25 mole of absolute ethanol were heated either alone or in the presence of 1 g. of sulfuric acid or 1 g. of sodium methoxide under reflux for eight hours no reaction took place. The starting materials were recovered quantitatively.

Heating Ethyl Orthoformate with Ethyl β-Acetoxycrotonate.—A mixture of 74 g. (0.5 mole) of ethyl orthoformate and 86 g. (0.5 mole) of ethyl β-acetoxycrotonate[12] was heated under reflux for three hours. The liquid became colored pale yellow but no reaction appeared to take place. After careful fractionation through a packed column there was obtained 72 g. (97%) of unchanged ethyl orthoformate, b.p. 138–145° and 80 g. (93%) of unchanged ethyl β-acetoxycrotonate, b.p. 80–88° (8 mm.).

The above experiment was repeated except that 2 ml. of boron trifluoride etherate was added. After fractionation of the liquid there was obtained 50 g. of distillate, b.p. 35–55°, which was identified as a mixture of ethyl ether and ethyl formate; 9 g. of ethyl orthoformate, b.p. 130–150°, and 75 g. (87%) of unchanged ethyl β-acetoxycrotonate, b.p. 86–88° (8 mm.).

This is evidence that ethyl β-acetoxycrotonate cannot be an intermediate in the reaction of ethyl acetoacetate with ethyl orthoformate and acetic anhydride to give ethyl ethoxymethyleneacetoacetate.

Reaction of Ethyl Triethoxyacetate with Ethyl Oxalacetate.—Fifty-five grams (0.25 mole) of ethyl triethoxyacetate and 47 g. (0.25 mole) of ethyl oxalacetate were heated together under reflux in an oil-bath at 140° for eight hours. Distillation of the reaction mixture gave 8.0 g. of ethanol, b.p. 76–80°; 2.0 g. of liquid, b.p. up to 85° (8 mm.); 65 g. of a mixture of unreacted ethyl oxalacetate and ethyl triethoxyacetate, b.p. 85–120° (8 mm.); and 18 g. of liquid, b.p. 170–185° (2 mm.). The latter, after redistillation, yielded 16 g. (20%) of ethyl α-ethoxy-γ-ketoaconitate,[11] b.p. 166–168° (1 mm.). This product was characterized by conversion of a sample to the copper salt of ethyl dioxalacetate, m.p. 172–173° (lit.[11] 174–175°). It was further characterized by reaction with hydrazine hydrochloride to yield triethyl 3,4,5-pyrazoletricarboxylate, m.p. 90–91°. When mixed with an authentic sample (see below) the melting point was also 90–91°.

Triethyl 3,4,5-Pyrazoletricarboxylate.—To a solution of 3 g. (0.03 mole) of hydrazine dihydrochloride in 20 ml. of water was added 7.9 g. (0.025 mole) of ethyl α-ethoxy-γ-ketoaconitate[11] followed by 25 ml. of ethanol. The mixture was shaken, and it became warm. After heating on the steam-bath for about 10 minutes the mixture was evaporated under vacuum to remove the alcohol. Water, 25 ml., was added, and the solution was extracted with two 50-ml. portions of ether. The ether solution was dried with magnesium sulfate and evaporated leaving a sirup which soon crystallized. The crude yield of triethyl 3,4,5-pyrazoletricarboxylate was 6.8 g. (95%) and after recrystallization from a benzene–petroleum ether mixture the yield was 5.0 g. (70%). A sample was again recrystallized from ether–petroleum ether, m.p. 90–91° (lit.[13] 91°).

Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.86. Found: C, 50.59; H, 5.76; N, 10.41.

(12) L. Claisen and E. Haase, *Ber.*, **33**, 1242 (1900).

(13) E. Buchner and C. Heide, *ibid.*, **34**, 345 (1901).

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Stereochemical Course of the Addition of Halogens to Cholesterol

BY J. B. ZIEGLER AND A. C. SHABICA

RECEIVED APRIL 7, 1952

Direct bromochlorination of the 5,6-double bond in cholesterol and a number of its derivatives, using the N-bromoacetamide–hydrogen chloride couple, has enabled the conclusive demonstration that the halogenation of steroids of this type proceeds through the non-Markownikoff attack of halide anion on an α-oriented cyclic intermediate of the halonium type. This confirms the conclusions reached by Barton.

In a recent paper Barton and Miller[1] clarified the nature of the mutarotation of ordinary, levorotatory cholesterol dibromide and certain of its derivatives which occurs in solution in certain solvents. They proved the ordinary cholesterol dibromide to be 5α,6β-dibromo-3β-cholestanol and the thermodynamically more stable dextrorotatory isomer to be 5β,6α-dibromo-3β-coprostanol.

These authors also proposed a mechanism for the formation and isomerization of ordinary cholesterol dibromide. They visualized the formation of this substance from cholesterol as proceeding through the intermediate 5,6β-bromonium ion, followed by Markownikoff attack by bromide anion to give the 5α,6β-dibromide. This may be designated as mechanism A (see Chart I) (Hal = Br). However, more recently,[2] following a suggestion of Fieser,[3] they have revised their views in favor of

(1) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).

(2) D. H. R. Barton, E. Miller and H. T. Young, *J. Chem. Soc.*, 2598 (1951).

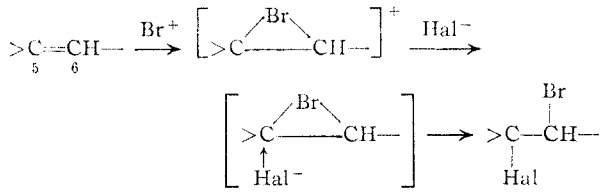
(3) L. F. Fieser, *Experientia*, **6**, 312 (1950).

a mechanism by which this compound is formed through non-Markownikoff addition of bromide anion to the intermediate 5,6α-bromonium ion. This may be termed mechanism B (see Chart I).

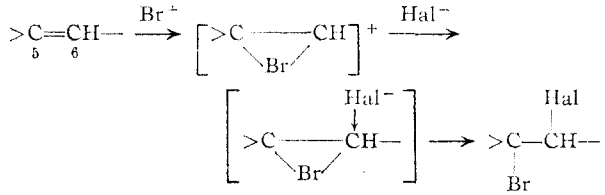
CHART I

Groups placed above the carbon–carbon axis are β-oriented; those below are α-oriented.

Mechanism A



Mechanism B



In 1950, we had completed experimental work which led us to the conclusion that this latter mechanism must necessarily be the correct one. In a number of its essential features, our method closely paralleled that of Barton and his colleagues[2]; however, as our work is distinguished by certain novel aspects, we wish to present it at this time as a confirmation of that of the British investigators.

Of crucial importance in their work was the preparation and proof of structure of 5α-bromo-6β-chloro-3β-cholestanol. This they accomplished by the reaction between thionyl chloride and 5α-bromo-3β,6β-cholestanediol, a substance of known structure. The position of the halogen atoms was established by oxidation of the 3-hydroxy-5,6-bromochloro compound to the corresponding 3-ketone followed by dehydrohalogenation to give the known 6β-chloro-4-cholestene-3-one,[4] which also served to confirm the β-orientation at position 6. Since it was known[5] that chlorination with thionyl chloride of a halohydrin proceeds *via* the intermediate halonium ion with complete retention of configuration, it is clear that the formation of the 5α-bromo-6β-chloro-3β-cholestanol as outlined above must have proceeded through the non-Markownikoff attack of chloride anion on the intermediate 5,6α-bromonium ion.

Our method of attack on this problem was similar, except that we prepared the crucial 5α-bromo-6β-chloro-3β-cholestanol by a method which was perhaps somewhat more direct and more closely analogous to a conventional halogenation. Recently, Buckles[6] found that the reaction between olefins and N-bromoacetamide (NBA) in chloroform in the presence of excess anhydrous hydrogen bromide led very rapidly to the formation of dibromides in high yield. These reactions were exothermic and clean-cut, and a number of considerations led Buckles to postulate them to be of a polar nature best interpreted as involving an ionic intermediate such as the bromonium ion which retains its steric identity. Powerful support for this view was found in the observation that *dl*-stilbene dibromide was formed in high yield from the reaction between NBA-hydrogen bromide couple and *cis*-stilbene. In each case investigated by Buckles, this couple produced the same dibromide as that afforded by bromine itself. It may, therefore, be assumed that the action of the NBA–HBr couple on olefins produces dibromides by a polar mechanism very similar to that generally accepted for brominations by molecular bromine, the positive bromine being furnished by the bromoamide and the bromide anion by the hydrogen bromide.

More recently, in a logical extension of his previous work, Buckles[7] found that chlorobromides were produced from olefins by the action of the NBA–hydrogen chloride couple.

Application of these observations to the cholesterol series shows that a 5α,6β-dihalide would be produced according to either mechanism A or mechanism B (Chart I) so that with bromine or with NBA–HBr the 5α,6β-dibromide should be produced in either case. We have, indeed, found that 5α,6β-dibromo-3β-cholestanyl acetate was formed in about 90% yield by the action of NBA–HBr on cholesteryl acetate, in accordance with expectation. However, it will also be seen that the corresponding reaction with NBA–HCl is of crucial mechanistic importance, since in this case mechanism A would produce the 5α-chloro-6β-bromo derivative while the 5α-bromo-6β-chloro compound would result from mechanism B. It has been found that the action of NBA–HCl on cholesterol, or its acetate, or benzoate produced the corresponding 5α-bromo-6β-chloro derivatives in good yield, thus establishing mechanism B. Their structure was established (compare Barton, *et al.*[2]) by mild chromic acid oxidation of the 3-ol to the ketone, which was then dehydrohalogenated to give the known 6β-chloro-4-cholestene-3-one.[2] Qualitative tests demonstrated the formation of large amounts of ionic bromide, but *no chloride*, in this reaction. The steric configuration of the bromine atom at position 5 follows by analogy from the established structure of the 5α,6β-dibromide formed by the action of NBA–HBr on cholesteryl acetate, and also from the application of Barton's method of molecular rotation differences,[1] the data for which are given in Table I. The molecular rotation differences for the bromochloro compounds are generally in quite good agreement with those for the 5α,6β-dichlorides and -dibromides.

Barton, *et al.*,[2] have noted that 5α-bromo-6β-chloro-3β-cholestanyl benzoate showed no tendency to undergo rearrangement in chloroform at room temperature; this behavior was similar to that of the corresponding 5α,6β-dichloride but in contrast to that of the corresponding 5α,6β-dibromide. We have found that no mutarotation occurred when 5α-bromo-6β-chloro-3β-cholestanyl acetate was refluxed in benzene solution, or when the corresponding free hydroxy compound was allowed to stand in

(4) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 370 (1950).
(5) H. J. Lucas and C. W. Gould, Jr., *ibid.*, **63**, 2541 (1941).
(6) R. E. Buckles, *ibid.*, **71**, 1157 (1949).
(7) R. E. Buckles, Abstracts, Div. Org. Chem., Am. Chem. Soc. Meeting, Sept., 1950, pp. 61N–62N.

TABLE I

Substance	[M]D[a] Alcohol	Acetate	Benzoate	Ketone	ΔAc[b]	ΔBz[b]	ΔKet[b]
5α,6β-Dichloro-3β-cholestanol[c]	−123	−145	−112	−123	−22	+11[d]	±0
5α,6β-Dibromo-3β-cholestanol[c]	−240	−271	−234	−245	−31	+6	−5
5α-Bromo-6β-chloro-3β-cholestanol[e]	−217	−234	−170	−225	−17	+47	−8
	(−237[g])		(−212[g])			(+25[g])	
5β,6α-Dibromo-3β-coprostanol[c]	+257	+212[e]	+532	...	−45	+275	...
5α,6α-Dichloro-3β-cholestanol[f]	+9	....	+67	...	...	+58	...

[a] All rotations in chloroform solution. [M]D = [α]D × mol. wt./100. [b] ΔAc is the molecular rotation difference on acetylation, ΔBz that on benzoylation and ΔKet that on oxidation. [c] Data derived from Barton and Miller.[1] [d] The value, +9, is recorded in error in Barton and Miller.[1] [e] Experimental section. [f] Data from Barton and Miller.[4] [g] Data derived from Barton, *et al.*[2]

chloroform solution for 75 hours at room temperature. This behavior is in agreement with Barton's postulate[1] that steric hindrance between the C_6-halogen atom and the C_{10}-methyl group in a steroid 5α,6β-dihalide furnishes the driving force for the stereochemical inversion to the 5β,6α-configuration.

It is of some interest to note that the method of mixed melting points proved to be of very limited usefulness in establishing the relationship between certain pairs of halides encountered during the course of this work. For example, while 6β-chloro-4-cholestene-3-one is known[2] to give a melting point depression with the 6α-chloro isomer, we have found that it does not depress the melting point of 6β-bromo-4-cholestene-3-one. Similarly, we have observed that the melting points of mixtures of: (a) 5α-bromo-6β-chloro-3β-cholestanyl acetate and the corresponding 5α,6β-dibromide, (b) 5α-bromo-6β-chloro-3-cholestanone and the corresponding 5α,6β-dibromo compound and (c) 5α-bromo-6β-chloro-3β-cholestanol and the corresponding 5α,6β-dichloro compound, show no depression.

Acknowledgments.—The authors are indebted to many of their colleagues in these laboratories, and especially to Dr. D. A. Prins, for helpful and stimulating discussions of this problem. The technical assistance of Mr. Robert Bagdon was very helpful.

Experimental[8]

General Procedure for N-Bromoacetamide–Hydrogen Halide Reactions.—In all cases, the hydrogen halide gas used was obtained direct from a cylinder.

A solution of 0.01 mole of the steroid in 30 ml. of chloroform was saturated with the appropriate dry hydrogen halide and then cooled to 10°. A warm (about 40°) solution of 0.01 mole of N-bromoacetamide in 25 ml. of chloroform was added portionwise to the steroid solution at 10–15° with stirring, keeping the reaction mixture saturated with hydrogen halide. After all of the bromoamide solution had been added, the mixture was warmed to room temperature and filtered to remove the white precipitate of diacetamide hydrohalide.[6] After washing the filtrate to neutrality with water and drying over anhydrous magnesium sulfate, the solvent was removed *in vacuo*. The residual orange gum was crystallized from ethyl acetate–methanol and, if necessary, recrystallized for further purification.

5α-Bromo-6β-chloro-3β-cholestanol.—This substance was prepared according to the general procedure given above, except that the fourfold amount of reagents and solvents was used. The hydrogen halide was HCl.

From 15.48 g. (0.04 mole) of cholesterol there was obtained 14.4 g. of product, m.p. 138–139° dec. after one recrystallization from ethyl acetate–methanol.

For analysis, a sample was recrystallized from ethyl acetate–methanol and dried for two hours at 75° *in vacuo* over P_2O_5; m.p. 138–139° dec., $[\alpha]^{23}D$ −43°; [M]D −217° [lit.[2] m.p. 146–147° dec., [α]D −47°].

Anal. Calcd. for $C_{27}H_{46}OClBr$: C, 64.60; H, 9.24; Br + Cl, 22.99. Found: C, 64.65; H, 9.01; Br + Cl, 22.81.

The melting point of a mixture of this substance with normal cholesteryl dichloride[4] (m.p. 142–143°) was 139–141° dec.

5α-Bromo-6β-chloro-3β-cholestanyl Acetate.—Prepared according to the general procedure using HCl. From 4.29 g. of cholesteryl acetate there was obtained 4.53 g. of product, elongated white prisms, m.p. 116–119°. This was recrystallized from ethyl acetate–methanol, chromatographed over activated alumina in petroleum ether (b.p. 30–60°) and again recrystallized from ethyl acetate–methanol; m.p. 118–120°.

A sample was dried for three hours at 57° *in vacuo* over P_2O_5 for microanalysis.

Anal. Calcd. for $C_{29}H_{48}O_2ClBr$: C, 64.01; H, 8.89; Br + Cl, 21.21. Found: C, 63.67; H, 8.60; Br + Cl, 21.05; $[\alpha]^{23}D$ −43°; [M]D −234°.

The melting point of a mixture of this material with normal cholesteryl acetate dibromide[1] (m.p. 113–116°) was 114.5–118°.

This substance was also prepared by acetylation of the 5α-bromo-6β-chloro-3β-cholestanol described above. A suspension of 0.5 g. of the alcohol in a mixture of 10 ml. of glacial acetic acid and 2.5 ml. of acetic anhydride was cooled to 10° and treated with 5 drops of 70% aqueous perchloric acid solution with shaking. The temperature rose rapidly to 20° and the needles of the alcohol were rapidly replaced by the plates of the acetate. After standing at room temperature for 0.5 hour with occasional shaking, excess water was cautiously added. The mixture was filtered, and the solid was washed with water, then with a little methanol and air-dried. The crude product weighed 0.55 g. and had m.p. 117–120°. The melting point of a mixture with an authentic specimen prepared by the bromochlorination of cholesteryl acetate (m.p. 118–120°) was 117–120°.

After three recrystallizations from ethyl acetate–methanol, a specimen was dried for two hours at 75° *in vacuo* over P_2O_5 for analysis. It melted sharply at 119–121°; $[\alpha]^{22}D$ −43°, [M]D −234°.

Anal. Calcd. for $C_{29}H_{48}O_2BrCl$: C, 64.01; H, 8.89. Found: C, 63.81; H, 8.58.

5α-Bromo-6β-chloro-3β-cholestanyl Benzoate.—Prepared according to the general procedure using HCl. From 4.41 g. of cholesteryl benzoate, there was obtained 4.49 g. of product, m.p. 119–122°. After three recrystallizations from ethyl acetate, the melting point had risen to 125–127° and was unchanged on further recrystallization from the same solvent. A sample was dried for microanalysis for four hours at 75° *in vacuo* over P_2O_5; m.p. 126–127.5°, $[\alpha]^{22}D$ −28°, [M]D −171° [lit.[2] m.p. 124–125°, [α]D −35°].

Anal. Calcd. for $C_{34}H_{50}O_2BrCl$: C, 67.37; H, 8.32; Br + Cl,[9] 19.04. Found: C, 67.63; H, 8.02; Br + Cl, 19.11.

(8) All melting points were determined in an electrically-heated metal block using a thermometer which was internally compensated for the stem correction. All optical rotations were determined in chloroform solution, usually on the specimen as prepared for microanalysis, and are rounded off to the nearest degree. The microanalyses were performed under the direction of Mr. L. Dorfman. Miss Verda Powell determined the ultraviolet absorption spectra and the optical rotations.

(9) Barton, *et al.*,[2] erroneously record this value to be 19.45%.

5α,6β-Dibromo-3β-cholestanyl acetate was prepared according to the general procedure using HBr. From 4.29 g. of cholesteryl acetate there was obtained 4.8 g. of the ordinary cholesteryl acetate dibromide, m.p. 114.5–118°, mixed with an authentic specimen (m.p. 114–116°), m.p. 114–116°.

5α-Bromo-6β-chloro-3-cholestanone.—To a suspension of 5.00 g. of 5α-bromo-6β-chloro-3β-cholestanol in 125 ml. of glacial acetic acid was added a solution of 1.25 g. of chromium trioxide in 2.5 ml. of water and the mixture was warmed at 55° for one hour with occasional stirring. A large excess of water was added, causing crystallization. The crystals were collected on a buchner funnel, washed with water and methanol and air-dried. The product weighed 4.5 g., m.p. 61.5° dec. After recrystallization *in the cold* from chloroform–methanol, the product had m.p. 64.5° dec. A sample was dried for microanalysis for two hours at room temperature *in vacuo* over P_2O_5; $[\alpha]^{23}D$ −45°, $[M]D$ −225°.

Anal. Calcd. for $C_{27}H_{44}OBrCl$: Br + Cl, 23.08. Found: Br + Cl, 23.08.

The melting point of a mixture of this substance with crude 5α,6β-dibromo-3-cholestanone (m.p. 69–70° dec.) was 64–65° dec.

Dehydrohalogenation of 5α-Bromo-6β-chloro-3-cholestanone.—A mixture of 3.00 g. of bromochlorocholestanone, 3.6 g. of anhydrous sodium acetate and 150 ml. of anhydrous ethanol was refluxed for one hour. The supernatant liquid was decanted from the inorganic salt precipitate and water was added to the hot solution to cloudiness. The solution was then cooled under the tap and the crystals were collected on a buchner funnel, washed with a little methanol and air-dried. The crude product so obtained weighed 2.39 g., m.p. 120–124°. After recrystallization from ethyl acetate–methanol in the cold, 1.28 g. of 6β-chloro-4-cholestene-3-one was obtained, fine white crystals, m.p. 128–129°. Vigorous effervescence began at 170°. Recrystallization from the same solvent did not alter the melting point. A sample was dried for microanalysis for two hours at room temperature *in vacuo* over P_2O_5; $[\alpha]^{23}D$ +13°; λ_{max} 241 mμ, ϵ_{max} 11,805 (alc.) [lit.[4] m.p. 129–130° dec.; $[\alpha]D$ +14°, +17°, λ_{max} 241 mμ, ϵ_{max} 15,100 (alc.)].

Anal. Calcd. for $C_{27}H_{43}OCl$: Cl, 8.46. Found: Cl, 8.83, 9.06.

A mixture of another preparation of this substance (m.p. 129–131°) with authentic 6β-chloro-4-cholestene-3-one[4] (m.p. 125–126°) had m.p. 128–130°.

The salt residue from the dehydrohalogenation reaction mixture was combined with the aqueous alcoholic mother liquor from the organic reaction product and the whole was concentrated to small volume *in vacuo*, precipitating a trace of organic matter. The mixture was treated with Norit and filtered. Qualitative tests[10] demonstrated the presence of large amounts of bromide ion but no chloride ion in the filtrate.

6β-Chloro-4-cholestene-3-one.—This substance was prepared according to the procedure of Barton and Miller.[4] After three recrystallizations from ethyl acetate–methanol, the fine, white crystals had m.p. 125–126°. At 200° the melt was pale brown in color with only slight effervescence.

6β-Bromo-4-cholestene-3-one.—This substance was prepared according to the procedure of Dane, *et al.*[11] It has been synthesized by Barton and Miller[1] by a different method.

After recrystallization from ethyl acetate–methanol, the substance had m.p. 129–130°. At about 140° the melt turned blue-black with vigorous effervescence. A mixture of this material with the 6β-chloro-4-cholestene-3-one just described had m.p. 128–133°.

5β,6α-Dibromo-3β-coprostanyl Acetate.—This substance was prepared by acetylation of the corresponding alcohol[1] with acetic anhydride in glacial acetic acid–perchloric acid according to the procedure described above for the acetylation of 5α-bromo-6β-chloro-3β-cholestanol.

From 0.8 g. of the alcohol there was obtained, after recrystallization from ethyl acetate-methanol, 0.67 g. of product in the form of stout, rod-like prisms, m.p. 97–100°. The analytical sample was dried for three hours at 57° *in vacuo* over P_2O_5; $[\alpha]^{24}D$ +36°, $[M]D$ +212°.

Anal. Calcd. for $C_{29}H_{48}O_2Br_2$: C, 59.18; H, 8.22; Br, 27.16. Found: C, 59.27; H, 8.18; Br, 27.32.

(10) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 116.

(11) E. Dane, Y. Wang and W. Schulte, *Z. physiol. Chem.*, **245**, 80 (1936).

SUMMIT, NEW JERSEY

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK & CO., INC.]

The Transformation of Manogenin to Hecogenin[1]

BY N. L. WENDLER, H. L. SLATES AND M. TISHLER

RECEIVED APRIL 10, 1952

The transformation of manogenin to Δ^2-22-isoallospirostene-12-one and thence to hecogenin is described.

The isolation of hecogenin from various *Agaves* (*e.g.*, *Agave toumeyana*) generally requires separation from a companion genin manogenin (I), wherein the latter is often present to the major extent.[2] Manogenin isolated by chromatographic methods is very difficult to separate from Δ^9-dehydromanogenin (Ia) which is present with it.[3] In order to obviate complications which would otherwise attend transformation reactions performed on such a mixture as well as to utilize as nearly as possible the total manogenin fraction involved, this mixture was converted by sodium–butanol reduction to the saturated triol, agavogenin (II). The latter in the form of its 2,3-dihemisuccinate derivative (III) was oxidized at position 12 with chromic acid followed by saponification to manogenin (I) in good over-all yield. It was subsequently ascertained that manogenin thus obtained was contaminated with varying amounts of gitogenin (Ib) which, nonetheless, could be easily and completely separated at a later stage (see below).

Manogenin free of Δ^9-dehydromanogenin and containing some gitogenin, was converted in high yield to the dimesylate derivative (IV) from which manogenin dimesylate could be obtained without

(1) Presented in part before the American Chemical Society Meeting-in-Miniature, Newark, N. J., January 28, 1952.

(2) Dr. J. W. Rothrock of these laboratories, to whom we are indebted for our supply of manogenin, has found the ratio of manogenin to hecogenin isolated from many samples of *Agave toumeyana* to average *ca.* 60:40, respectively.

(3) R. B. Wagner, R. F. Forker and P. F. Spitzer (THIS JOURNAL, **73**, 2494 (1951)) have isolated Δ^9-dehydromanogenin by chromatography of manogenin fractions isolated from *Agave huachucensis*. These authors have estimated by ultraviolet absorption measurements that the content of Δ^9-dehydromanogenin in manogenin fractions isolated from various *Agaves* to range from 20–80%. Our own observation, made with certain manogenin fractions isolated from *Agave toumeyana*, indicated a content of Δ^9-dehydromanogenin in the order of 40–50%.