anthrene,[21] 0.4 g. of sodium hydroxide, 10 ml. of ethanol and 2.0 g. of Raney nickel was shaken in a hydrogen atmosphere at 3000 p.s.i. and 100° for 24 hr. The mixture was filtered through a Celite mat and the solution concentrated to dryness. The residue was dissolved in 20 ml. of benzene and chromatographed on ethyl acetate-washed alumina. Elution with benzene yielded 1.1 g. of **2-hydroxy-*sym*-octahydrophenanthrene** with a low melting point. Distillation of this material at a bath temperature of 180° and 0.5 mm. and crystallization from ether afforded 0.9 g. of white needles, m.p. 128–129.5° (capillary m.p., corrected).

(21) We are grateful to Dr. R. C. Elderfield for a generous supply of this material.

Anal.[22] Calcd. for $C_{14}H_{18}O$: C, 83.1; H, 9.0. Found: C, 83.1; H, 9.1.

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(22) The microanalysis is by the Analytical Service Laboratory of this Institute under the direction of Dr. William C. Alford.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Bromination of 5α,6β-Dibromocholestane-3-one

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Reinvestigation of the bromination of 5α,6β-dibromocholestane-3-one has shown that the initial products, depending upon the conditions, are the 2α- and 2β-bromo derivatives II and III and that further bromination affords the 2α,2β,5α,6β-derivative IV. The structures were established largely by dehydrohalogenations conducted with collidine under non-rearrangement conditions; the configurations of the bromine substituents were established by synthetic operations. Transformations of the bromo ketones are accounted for, and the structures and configurations assigned accord with established ultraviolet and infrared absorption data.

In 1936, Inhoffen[1] and Butenandt and Schramm[2] investigated the monobromination of 5α,6β-dibromocholestane-3-one[3] (I) under slightly different conditions and obtained different tribromo ketones. Inhoffen's product, m.p. 138°, resulted from bromination in ether–acetic acid; Butenandt and Schramm's product, 106°, was obtained by bromination in acetic acid alone. Since both tribromo ketones on further bromination yielded the same tetrabromo ketone they were regarded as stereoisomers, an inference confirmed by Corey's observation[4] that the lower-melting tribromo ketone is converted by ethereal hydrogen chloride into the higher-melting isomer.

Both Inhoffen and Butenandt and Schramm regarded the two epimeric tribromo ketones as 4,5,6-derivatives and the tetrabromo ketone as the 4,4,-5,6-derivative mainly on the apparent evidence of three transformations. One was conversion of both tribromo ketones by the action of boiling ethanol into 6-ethoxy-$\Delta^{4,6}$-cholestadiene-3-one, the enol ethyl ether of Δ^4-cholestene-3,6-dione.[1,2] A second was formation of cholestane-3,6-dione in 60% yield from the lower-melting tribromo ketone on treatment with sodium iodide followed by reaction with potassium acetate (200°, five hours).[2] The third transformation considered to support the postulated structures was conversion of Inhoffen's tribromo ketone and of the tetrabromo ketone on drastic treatment with potassium acetate into the enol acetate of diosterol-II, at the time formulated as 4-acetoxy-$\Delta^{4,6}$-cholestadiene-3-one, but now considered to be 3-acetoxy-$\Delta^{2,5}$-cholestadiene-4-one.[5] The second and third transformations involve reaction with potassium acetate at a high temperature, which is now known to be accompanied rather frequently by rearrangement.[6] The only reaction with potassium acetate at room temperature reported was that of Inhoffen's tribromo ketone. The product, originally formulated as 4,6-dibromo-Δ^4-cholestene-3-one, has since been shown to be a 2,6-dibromo-Δ^4-cholestene-3-one,[7] and hence this evidence favors location of the bromine introduced by substitution at position 2 rather than 4.

Another reason for questioning the original formulations is that bromination of A/B *trans* 3-ketones ordinarily gives rise to 2-bromo derivatives, even when the 5α-hydrogen is replaced by a substituent, such as a hydroxyl group.[8] Moreover the ultraviolet absorption characteristics of the transformation products are such as to throw some doubt on the assigned structures.[9]

Since dehydrohalogenation with collidine is seldom attended with rearrangements,[10] we have studied the reaction of the polysubstituted ketones with this reagent. The results show that the tribromo ketones are 2,5,6-derivatives. Brief treatment of either isomer II or III with collidine results in elimination of two equivalents of hydrogen bromide with formation of a bromodienone, which has

(1) H. H. Inhoffen, *Ber.*, **69**, 1134, 1702 (1936).

(2) A. Butenandt and G. Schramm, *ibid.*, **69**, 2289 (1936).

(3) The configuration of the bromine atoms since has been established by D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).

(4) E. J. Corey, *ibid.*, **76**, 175 (1954).

(5) L. F. Fieser, M. Fieser and S. Rajagopalan, *J. Org. Chem.*, **13**, 800 (1948).

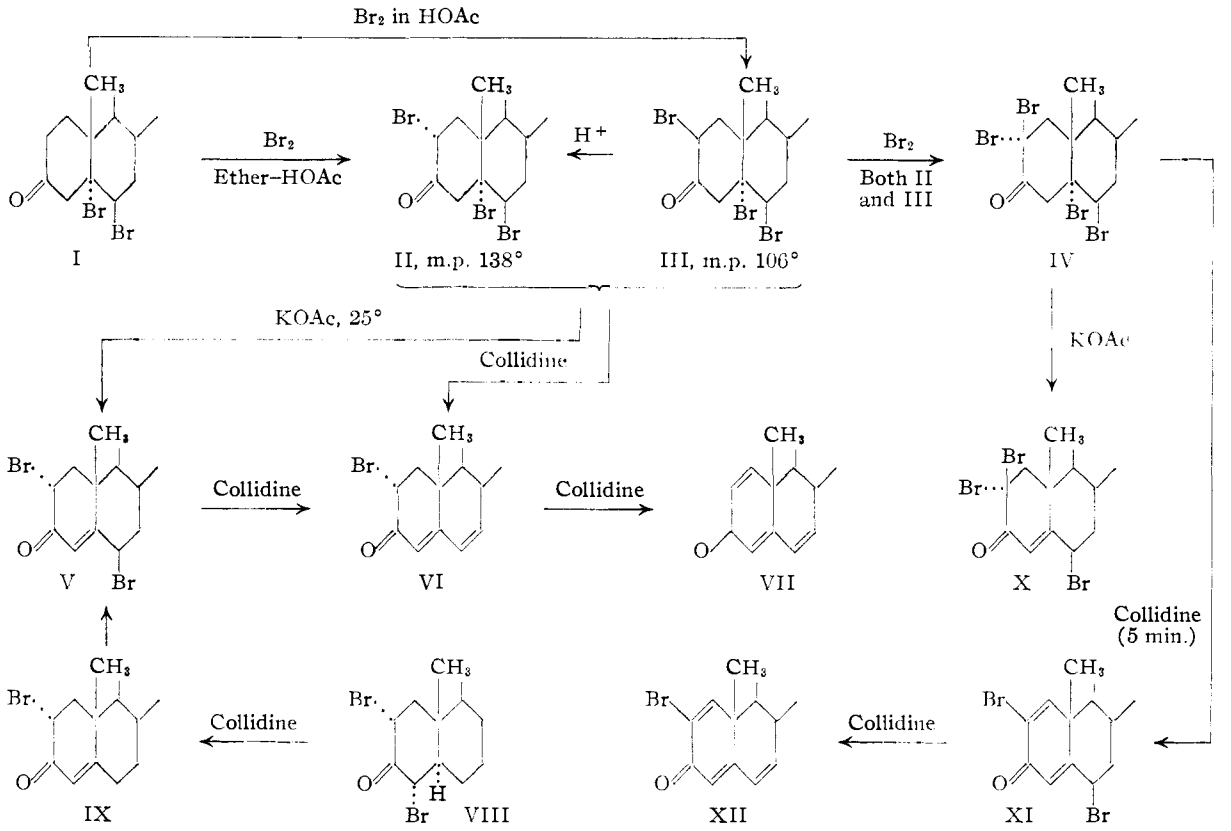
(6) Examples: 2α-bromocholestane-3-one → Δ^4-cholestene-4-one, A. Butenandt and G. Ruhenstroth-Bauer, *Ber.*, **77**, 397 (1944); 2α,4α-dibromocholestane-3-one → cholestane-3,4-dione; 2-bromo-5-chlorocholestane-3-one → cholestane-3,6-dione and cholestane-3,4-dione, A. Butenandt, G. Schramm, A. Wolff and H. Kudszus, *ibid.*, **69**, 2779 (1936); 6β-bromo-Δ^4-cholestene-3-one → 2α-acetoxy-Δ^4-cholestene-3-one, L. F. Fieser and M. A. Romero, THIS JOURNAL, **75**, 4716 (1953).

(7) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, *ibid.*, **72**, 4534 (1950).

(8) B. Ellis and V. Petrow, *J. Chem. Soc.*, 1078 (1939); 2194 (1950).

(9) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(10) Dehydrohalogenation of 2α-bromochloestane-3-one with collidine affords Δ^4-cholestene-3-one as a minor product (12–23% yield), but the major product is the expected Δ^1-cholestene-3-one; C. Djerassi and C. Schultz, THIS JOURNAL, **69**, 2404 (1947).



an absorption maximum at 290 mμ (25,000), close to that of $\Delta^{4,6}$-cholestadiene-3-one, λ 283–284 (26,300). The bromine atom cannot be on the unsaturated system at 4 or at 6, since such substitution would produce a bathochromic shift of at least 25 mμ.[11] That the product is actually a 2-bromo-$\Delta^{4,6}$-cholestadiene-3-one (VI) is shown by further dehydrohalogenation with collidine to $\Delta^{2,4,6}$-cholestatriene-3-one (VII), identified by the typical triple maxima in the ultraviolet and by comparison with a sample prepared according to the literature.[7]

The tribromo ketones are thus 2,4,6-derivatives, epimeric at C_2. That the more stable tribromo ketone, m.p. 138°, has the expected equatorial (α) orientation was established by a synthesis starting with 2α,4α-dibromocholestane-3-one[12] (VIII). Brief treatment of VIII with collidine affords 2α-bromo-Δ^4-cholestene-3-one[13] (IX), which on bromination with N-bromosuccinimide gave a dibromocholestenone identical with the product of monodehydrohalogenation of both tribromo ketones (II and III) with potassium acetate at room temperature. The compound is evidently 2α,6β-dibromo-Δ^4-cholestene-3-one (V).

The results of collidine dehydrohalogenations are consistent with formulation of the tetrabromo ketone as 2α,2β,5α,6β-tetrabromocholestane-3-one (IV). On brief treatment (5 min.) with collidine two equivalents of hydrogen bromide are eliminated with formation of a dibromocholestadienone having an absorption band at 253 mμ (17,700), corresponding to that of known 2-bromo-$\Delta^{1,4}$-3-ketones.[8] We thus formulate the product as 2,6β-dibromo-$\Delta^{1,4}$-cholestadiene-3-one (XI). Prolonged dehydrohalogenation gives a product which, because it has ultraviolet absorption characteristic of $\Delta^{1,4,6}$-trienones, can be formulated as 2-bromo-$\Delta^{1,4,6}$-cholestatriene-3-one (XII). Dehydrohalogenation of the tetrabromo ketone IV with potassium acetate at room temperature gave 2α,2β,6β-tribromo-Δ^4-cholestene-3-one (X), identical with a compound prepared by Butenandt, Schramm and Kudszus[14] by bromination of V. These authors formulated the substance as 4,6,6-tribromo-Δ^4-cholestene-3-one (formula VII of their paper) but such a structure should exhibit absorption at about 270 mμ, whereas the observed value is 253 mμ (ether). Revised formulas now can be assigned to a series of transformation products described in the same paper. The dibromodienone (their XII), m.p. 183°, λ^{Chf} 296 mμ (19,400) is 2α,2β-dibromo-$\Delta^{4,6}$-cholestadiene-3-one; the tribromodienone (their XIII), m.p. 166°, λ^{Chf} 313 mμ (17,400) is 2α,2β,6-tribromo-$\Delta^{4,6}$-cholestadiene-3-one; and the dibromotrienone (their XIV), m.p. 203°, is then 2,6-dibromo-$\Delta^{1,4,6}$-cholestatriene-3-one, as tentatively suggested by Inhoffen and Becker.[15]

The present structures are not inconsistent with the transformations noted above. The reaction of

(11) See A. L. Nussbaum, *et al.*, THIS JOURNAL, **73**, 3263 (1951).

(12) For the orientation of the bromine atoms see R. N. Jones, *et al.*, *ibid.*, **74**, 2828 (1952).

(13) C. Djerassi, *ibid.*, **71**, 1003 (1949). This readily occurring dehydrohalogenation probably proceeds through partial epimerization at C_4.

(14) A. Butenandt, G. Schramm and H. Kudszus, *Ann.*, **551**, 176 (1937).

(15) H. H. Inhoffen and W. Becker, *Ber.*, **85**, 183 (note 5) (1952).

the tribromo ketones II and III with boiling ethanol may involve formation of the unsaturated dibromo ketone V and allylic migration of bromine through the enol from C_2 to C_6 to give 6,6-dibromo-Δ^4-cholestene-3-one, hydrolysis to Δ^4-cholestene-3,6-dione, and acid-catalyzed enol ether formation. The reaction of III with sodium iodide and then potassium acetate to form cholestane-3,6-dione may proceed by 5,6-debromination, migration of bromine from C_2 to C_4 to C_6, hydrolysis to 6β-hydroxy-Δ^4-cholestene-3-one, and isomerization. Related reactions are the conversion of 5α,6β-dibromocholestane-3-one into cholestane-3,6-dione[16] and of 2-bromo-6β-acetoxycholestane-5α-ol-3-one into Δ^4-cholestene-3,6-dione.[8] A possible path for the transformation of the tribromo ketone III into 3-acetoxy-$\Delta^{2,5}$-cholestadiene-4-one is: dehydrohalogenation to V, allylic migration of bromine from C_6 to C_4, migration of the bromine at C_2 through the enol to C_4 to give 4,4-dibromo-Δ^5-cholestene-3-one, followed by the reactions of acetolysis and acyl migration previously postulated for the same intermediate.[5]

The present structures are also consistent with known effects of substitution of halogen adjacent to a carbonyl group on the infrared carbonyl stretching band.[17] A bromine atom of equatorial orientation produces a slight shift in the position of the carbonyl band, whereas if the orientation is axial the effect is negligible. The effects noted with the bromo ketones considered in this paper are summarized in Table I.

TABLE I

EFFECT OF BROMINE SUBSTITUTION ON INFRARED CARBONYL ABSORPTION

Bromo ketone	Conformation of α-Br	Shift, Δλ, μ
2α-Bromo-Δ^4-cholestene-3-one (IX)	Equatorial	0.07
2α,6β-Dibromo-Δ^4-cholestene-3-one (V)	Equatorial	.08
2α,5α,6β-Tribromocholestane-3-one (II)	Equatorial	.06
2β,5α,6β-Tribromocholestane-3-one (III)	Axial	.02
2α,2β,6β-Tribromo-Δ^4-cholestene-3-one (X)	Equat., axial	.05
2α,2β,5α,6β-Tetrabromocholestane-3-one (IV)	Equat., axial	.05

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Experimental

2α,6β-Dibromo-Δ^4-cholestene-3-one (V). (a) From 2α,5α,6β- and 2β,5α,6β-Tribromocholestane-3-one (II and III).—The partial dehydrohalogenation of the tribromo ketones with potassium acetate in ethanol–benzene was carried out as described by Inhoffen[1] for II. The product (V) was the same in both cases (yield about 75%).

(16) E. Dane, Y. Wang and W. Schulte, *Z. physiol. Chem.*, **245**, 80 (1937).

(17) R. N. Jones, *et al.*, THIS JOURNAL, **72**, 956 (1950); **74**, 2828 (1952).

(b) **From 2α-Bromo-Δ^4-cholestene-3-one (IX).**—The bromo ketone (200 mg.), prepared according to Djerassi,[13] was treated with N-bromosuccinimide (80 mg.) in refluxing carbon tetrachloride (30 ml.) under illumination. After evaporation of the solvent under reduced pressure, the residue was crystallized from aqueous acetone; the product (V, 180 mg., 77% yield) was obtained as long colorless needles, m.p. 169–170°, α_D^{Chf} +50.0 ± 2°, λ^{EtOH} 248 mμ (14,100), λ^{Chf} 5.91 μ.

2α-Bromo-$\Delta^{4,6}$-cholestadiene-3-one (VI). (a) From 2α,6β-Dibromo-Δ^4-cholestene-3-one (V).—A solution of the dibromo-Δ^4-3-ketone (2 g.) in freshly distilled collidine (8 ml.) was refluxed for 15 min. and then cooled. The collidine hydrobromide was removed by filtration, and the solution, diluted with ether, was washed with dilute hydrochloric acid and then water. The ethereal solution was dried with anhydrous sodium sulfate and evaporated. The residue on crystallization from petroleum ether–benzene gave the bromodienone VI (1 g., 59% yield) as yellowish prisms, m.p. 146–147° dec., λ^{EtOH} 290 mμ (25,000), λ^{Chf} 6.01, 6.20, 6.33 μ.

Anal. Calcd. for $C_{27}H_{41}OBr$ (461.51): C, 70.10; H, 8.93; Br, 17.27. Found: C, 70.46; H, 9.04; Br, 17.38.

(b) **From 2α,5α,6β-Tribromocholestane-3-one (II).**—A solution of the tribromo ketone (3 g.) in distilled collidine (20 cc.) was refluxed for 30 min. The reaction was worked up as in (a). The bromodieneone VI was obtained (400 mg., 18% yield).

(c) **From 2β,5α,6β-Tribromocholestane-3-one (III).**—The dehydrohalogenation was carried out as in (b) and the product VI was obtained in 22% yield.

$\Delta^{1,4,6}$-Cholestatriene-3-one (VII).—A solution of 2-bromo-$\Delta^{4,6}$-cholestadiene-3-one (240 mg.) in collidine (2 ml.) was refluxed for 5 hr. The reaction mixture was worked up in the usual way, and the trienone (VII) was obtained in 56% yield as a low-melting solid; neg. Beilstein test; λ^{EtOH} 224 mμ (10,700), 258 mμ (8300), 300 mμ (12,860).

The same material was obtained (31% yield) from 2α,6β-dibromo-Δ^4-cholestene-3-one (V) as already reported.[7]

2,6β-Dibromo-$\Delta^{1,4}$-cholestadiene-3-one (XI).—The tetrabromo ketone IV (500 mg.) was heated in distilled collidine to reflux for 10 min., and the reaction was then worked up by the usual procedure. The crude product was chromatographed through alumina, and the petroleum ether–benzene (5:3) eluate afforded 180 mg. (47% yield) of colorless needles, m.p. 177–178°. Pure XI was obtained by crystallization from aqueous acetone; m.p. 180–181° dec., α_D −55 ± 2° (Chf), λ^{EtOH} 253 mμ (17,800), λ^{Chf} 6.03, 6.25 μ.

Anal. Calcd. for $C_{27}H_{41}OBr_2$ (541.43): C, 59.88; H, 7.63; Br, 29.52. Found: C, 60.48; H, 8.21; Br, 29.72.

2-Bromo-$\Delta^{1,4,6}$-cholestatriene-3-one (XII).—The tetrabromo ketone IV (2 g.) was dehydrohalogenated in the usual way in collidine (15 ml., 1.5 hr. reflux). The product, m.p. 145–146°, 53% yield, crystallized from petroleum ether as straw-colored needles, m.p. 148–149° dec., α_D −16 ± 1° (Chf), λ^{EtOH} 224 mμ (14,780), 271 mμ (12,000), 308 mμ (9750), λ^{Chf} 6.08, 6.25, 6.32 μ.

Anal. Calcd. for $C_{27}H_{31}OBr$ (460.50): C, 70.41; H, 8.53; Br, 17.35. Found: C, 70.11; H, 8.39; Br, 17.51.

2,2,6β-Tribromo-Δ^4-cholestene-3-one (X).—The tetrabromo ketone IV (2 g.), dissolved in a mixture of absolute ethanol (70 ml.) and benzene (30 ml.), was treated with potassium acetate (0.4 g.); the reaction mixture was allowed to stand for 24 hr. at room temperature. Potassium bromide separated and was removed by filtration; the solvent was evaporated under reduced pressure and the solid residue crystallized from acetone (1.2 g., 68% yield); m.p. 185–186°, α_D −6 ± 1° (Chf), λ^{Chf} 5.96, 6.21 μ.

The product was shown by direct comparison to be identical with Butenandt's "Δ^4-cholestenone-3-tribromide-4,6,-6," a sample of which was prepared from V by his procedure.[14]

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