The non-ketonic fractions were washed with a small amount of ether to remove oily products. They were then crystallized from methanol to give products melting in the range of 205–208°. A mixture with tigogenin gave no depression. Yields were 8.3–14.7 g.

*Anal.* Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.7. Found: C, 78.0; H, 10.6.

Acetylation and crystallization from methanol gave tigogenin acetate, m. p. and mixed m. p. 204°.

*Anal.* Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 76.1; H, 9.9.

The mother liquors from the crystallization of tigogenin were concentrated and the residue was crystallized from ether to give gitogenin, m. p. and mixed m. p. 266–268°. Yields were 4.6–8.1 g.

*Anal.* Calcd. for $C_{27}H_{44}O_4$: C, 75.0; H, 10.3. Found: C, 75.0; H, 10.1.

Acetylation and crystallization from methanol gave gitogenin diacetate, m. p. and mixed m. p. 242°.

*Anal.* Calcd. for $C_{31}H_{48}O_6$: C, 72.1; H, 9.4. Found: C, 72.1; H, 9.6.

No other steroidal sapogenins could be isolated from the mature plants.

## Summary

Young plants of *Agave atrovirens, Agave bracteosa, Agave endlichiana, Agave stricta, Agave mitraeformis, Manfreda gigantea* and *Hesperaloe funifera* gave only manogenin as their steroidal sapogenin. When the plants reached maturity this was converted into hecogenin, gitogenin and tigogenin.

TEXCOCO, MEXICO RECEIVED OCTOBER 21, 1946

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

# The Bromination of 3-Ketosteroids in Acetic Acid and the Effect of Trace Substances in the Solvent

BY CARL DJERASSI AND CAESAR R. SCHOLZ

Recently, it was noted[1] that the course and the rate of the dibromination of androstan-17$\alpha$-ol-3-one 17-hexahydrobenzoate (Ia) in acetic acid was dependent to a large extent on whether the acetic acid had been distilled from permanganate. No details were given. Since brominations are used widely in steroid chemistry and are generally performed in acetic acid, we have studied more closely the effect of trace substances in the acetic acid on the bromination of four 3-ketosteroids of the *allo* series.

Since it had been found[1] that the rotations of the two isomeric dibromo ketones IIIa and IVa differed widely, it was possible to follow the course of the dibromination of the ketone Ia polarimetrically, similar to the determination of the mutarotation of sugars. The results of the polarimetric studies are summarized in Fig. 1 and Table I. Using C. P. glacial acetic acid, it was found that within five minutes the rotation of the solution rose to a maximum of +110° at the time of decolorization and then the rotation receded. The time required to reach this point of regression gave a quantitative measure of the rate of dibromination. Raising the temperature or adding hydrogen bromide caused the bromination to proceed so rapidly that this maximum could not be observed (*cf.* Fig. 1). However, when acetic acid was used which had been distilled from potassium permanganate or chromic trioxide, the bromination was very slow and nearly four hours were required for the rotation to reach its maximum value. As was to be expected, the addition of hydrogen bromide increased the rate of bromination, but more hydrogen bromide had to be added to obtain the same results as with C. P. acetic acid.

(1) Wilds and Djerassi, THIS JOURNAL, **68**, 2125 (1946); *cf.* footnote 22a.

The polarimetric study also afforded a means of following the rate of rearrangement of the 2,2-dibromo ketone IIIa to the 2,4-isomer IVa. In C. P. acetic acid, the "half life"[2] of the 2,2-dibromo compound IIIa was approximately one hour, but could be decreased enormously by raising the temperature or by adding hydrogen bromide. In acetic acid distilled from permanganate, the rate of rearrangement was very slow (half life of *ca.* eighteen hours); this behavior could be duplicated in C. P. acetic acid which had not been distilled from permanganate by adding sodium acetate or 30% hydrogen peroxide at the end of the bromination.

On first thought, it appeared that small amounts of peroxide or peracid were formed during the oxidative treatment, which removed some of the hydrogen bromide liberated and thus slowed the rate of bromination and rearrangement. This possibility was excluded, however, by the observation that addition of reducing agents such as Raney nickel or sodium bisulfite to the acetic acid, followed by distillation, did not remove the inhibitor, nor was it affected by long refluxing or several distillations. Furthermore, the presence of peroxide could not be demonstrated iodometrically. The addition of small amounts of heavy metal salts, especially those of chromium and manganese to C. P. acetic acid had no definite effect on the rate of reaction and thus eliminated the possibility that some of the oxidizing agent was carried over into the distillate. The problem was finally solved when C. P. acetic acid andC. P. acetic acid distilled from permanganate was fractionated through a thirty-plate column. These results are summarized in Table I. The impurity was con-

(2) The term "half life" denotes the time required for the rotation of the solution to drop from +110 to +58°, since the total change in rotation is 116° (+110 to −6°).

centrated in the first fraction and was identified as water. Quantitative determination of the water by means of Karl Fischer reagent demonstrated that distillation of the acetic acid over permanganate resulted in a ten-fold increase of the water content and that the rate of bromination and of rearrangement could be strictly correlated with the amount of water present (Table I). This increase in the water content was very probably due to the oxidation of part of the acetic acid, since the C. P. potassium permanganate used was anhydrous. These results are in good agreement with the observation of Cohen[2a] who noted the inhibitory influence of small amounts of water on the bromination of acetone in carbon tetrachloride. The addition of as little as 0.1 cc. of water to 15 cc. of pure, fractionated glacial acetic acid increased the time required for complete dibromination from five to fifty-three minutes and the half life[2] from fifteen minutes to three hours. Water, acting as a base, probably affects the degree of enolization of the ketone, which seems to be the rate-determining step in both the bromination and rearrangement, by decreasing the acid strength of the hydrogen bromide catalyst.

We have also studied the rearrangement of the 2,2-dibromo compound IIIa to the 2,4-isomer IVa[1,3] in the *absence* of *added hydrogen bromide*. It was found that when the pure 2,2-isomer IIIa was dissolved quickly in C. P. acetic acid by heating and the solution cooled immediately, the dibromo ketone IIIa was recovered unchanged. When heated for three minutes or longer, rearrangement had occurred, as demonstrated by the determination of the rotation of the solution and the isolation of the 2,4-isomer IVa. The rearrangement was inhibited by the addition, *prior* to the heating, of small amounts of sodium acetate or hydrogen peroxide. These results suggest the formation of small amounts of hydrogen bromide arising from dehydrobromination of the 2,2-isomer, which are sufficient to catalyze the rearrangement at the elevated temperature (*cf.* Fig. 1 for effect of temperature on rearrangement).

It is interesting to note that in the presence of sufficient hydrogen bromide, the bromine atom in the vinyl bromide type of compound VIIa could be made to migrate. Although $\Delta^1$,4-bromoandrosten-17$\alpha$-ol-3-one 17-hexahydrobenzoate was not obtained in pure form, its structure was proven by its absorption spectrum and the lability of the bromine atom toward collidine, leading to 1,4-androstadien-17$\alpha$-ol-3-one 17-hexahydrobenzoate (IXa), in contrast to the starting material VIIa, which had been shown to be resistant to dehydrobromination.[1,3]

To determine the applicability of these results to other steroids, several ketones of the *allo* series were selected. Androstan-17$\alpha$-ol-3-one 17-acetate (Ib) gave the same results as the hexahydro-

(2a) Cohen, THIS JOURNAL, **52**, 2827 (1930).

(3) Inhoffen and Zuehlsdorff, *Ber.*, **76**, 233 (1943).

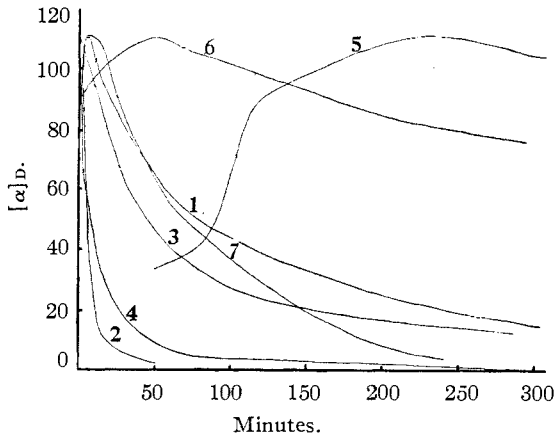



Fig. 1.—Dibromination of Ia: (1) C. P. glacial acetic acid at 23°; (2) as in 1, but at 48°; (3) as in 1, but with addition of 15 mg. of hydrogen bromide; (4) with addition of 75 mg. of hydrogen bromide; (5) acetic acid distilled from permanganate; (6) as in 5, with addition of 15 mg. of hydrogen bromide; (7) as in 5, with addition of 300 mg. of hydrogen bromide.

benzoate Ia. By applying the methods to cholestanone (Ic), it was shown that the dibromination proceeds similarly, and it was possible to isolate the intermediate 2,2-dibromocholestanone (IIIc), m. p. 145–147°, $[\alpha]^{22}D$ +104°.[4] Its structure was proved by an independent preparation from 2-bromocholestanone (IIc) and dehydrobromination to $\Delta^1$,2-bromocholestenone (VIIc).[5]

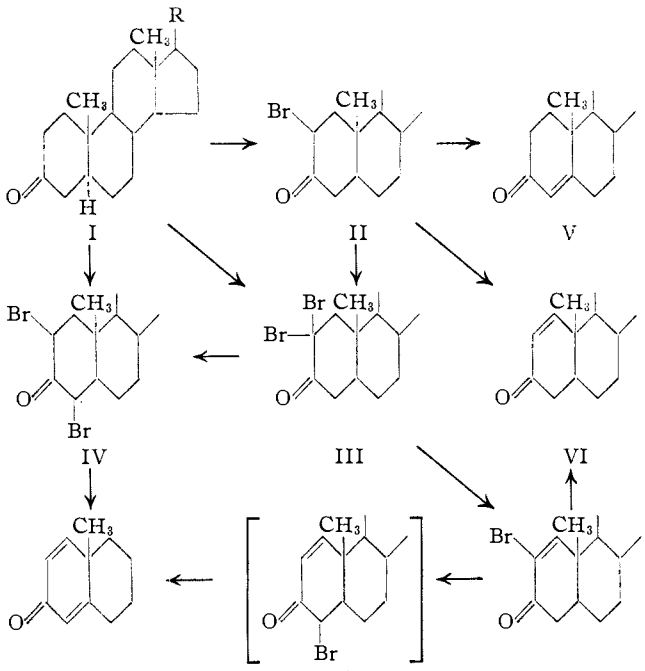
Since the position of the bromine atom in 2-bromocholestanone (IIc) was previously established[6] and the dehydrobromination experiment (IIIc → VIIc) indicates that the bromines are in a *gem* position, the structure must be that of the 2,2- rather than the 4,4-dibromo derivative.

(4) Doree, *J. Chem. Soc.*, 648 (1909), isolated a compound of m. p. 139–140° from the bromination of cholestanone in chloroform, and Ralls, THIS JOURNAL, **60**, 1744 (1938), obtained a dibromocholestanone of m. p. 147° on treating Ic with iodine monobromide. Both compounds are probably identical. It has been mentioned (ref. 3, p. 234, footnote 3) that the structure of Doree's compound was that of the 2,2-dibromo derivative IIIc, but no details were given.

(5) It may be noted that the position of the absorption maxima of these bromo ketones VII is apparently not in accord with Woodward's rule [THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942)], since they occur at 255–256.5 m$\mu$ for VIIa, c and d, rather than around 235 m$\mu$ as would be predicted by the rule for an unsaturated ketone with $\alpha$ and $\beta$ substituents and no exocyclic double bond. According to Woodward, a maximum at 255 m$\mu$ would indicate a $\Delta^4$,4-bromo-3-keto structure, but such a formula is incompatible with the zinc debromination of VIIa to $\Delta^1$-testosterone hexahydrobenzoate (VIa) as reported by Inhoffen und Zuehlsdorff (ref. 3). Under those conditions, a $\Delta^4$,4-bromo-3-keto derivative should yield testosterone hexahydrobenzoate (Va). In view of the importance of this debromination, and since no yield had been reported, we have repeated the reaction and have been able to isolate the $\Delta^1$-derivative VIa in 57% yield by a modification of the original procedure. The above absorption spectra results constitute an exception to Woodward's rule only, if the effect of a halogen substituent is considered equivalent to that of an alkyl group, an assumption which is probably not justified.

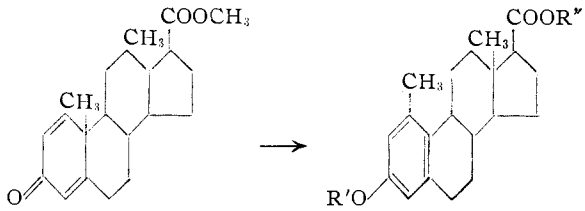
(6) Butenandt, Mamoli, Dannenberg, Masch and Paland, *Ber.*, **72**, 1617 (1939), reported the dehydrobromination of IIc to $\Delta^1$-cholestenone (VIc).

Jacobsen[7] reported that Butenandt's reaction[6] also gave rise to cholestanone and that $\Delta^1$-cholestenone was obtained only in poor yield. We have repeated the reaction under Butenandt's conditions and obtained the $\Delta^1$-compound VIc as the major product accompanied by appreciable amounts of $\Delta^4$-cholestenone (Vc) by rearrangement but no cholestanone was produced. Similar results were obtained with IIa, where nearly 20% of testosterone hexahydrobenzoate (Va) was isolated. The conversion of a 2-bromo-3-keto*allo*steroid to the corresponding $\Delta^4$,3-keto-derivative previously has been accomplished[8] by thermal decomposition of the pyridinium salt. The reason this reaction also occurs in collidine might be due to the formation of a collidinium salt, which is decomposed under conditions somewhat milder than those prevailing for the corresponding pyridinium salt. Another method of converting a 3-keto*allo*steroid to the corresponding $\Delta^4$,3-keto derivative is illustrated in the experimental section by the following sequence of reactions: saturated ketone Id → 2,4-dibromo ketone IVd → $\Delta^4$,2-bromo-3-keto derivative → $\Delta^4$,3-ketosteroid Vd.



(a) R = $OCOC_6H_{11}$ (c) R = $C_8H_{17}$
(b) R = $OCOCH_3$ (d) R = $COOCH_3$

Essentially the same results were obtained in the bromination of methyl 3-keto*allo*etiocholanate (Id). When the "dienone-phenol rearrangement"[9] was applied to compound IXd, it readily gave the corresponding phenol acetate X and on saponification the phenol XI.



IXd

X R′ = $CH_3CO$; R″ = $CH_3$
XI R′ = R = H

The aromatic structure is supported by the characteristic ultraviolet absorption of the acetate X and of the phenol XI (Fig. 2), as well as by the high positive rotation, as previously observed.[1,10]

The very capable assistance of Helen Dudek, Ann Pellet and Jean Rogers is gratefully acknowledged.

## Experimental[11,12]

### Bromination of Androstan-17α-ol-3-one Derivatives

**Androstan-17α-ol-3-one 17-Hexahydrobenzoate (Ia).**—The ketone Ia was prepared as previously described by oxidation of androstane-3β,17α-diol 17-hexahydrobenzoate.[1] From the alkaline washes on acidification and recrystallization from hexane–acetone, there was isolated colorless crystals of **2||3-androstan-17α-ol-2,3-diacid 17-hexahydrobenzoate**[13,14] with m. p. 209.5–211.5°, $[\alpha]^{23}D$ +24.9° (chloroform).

*Anal.* Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99; neut. equiv., 224.3. Found: C, 69.23; H, 8.89; neut. equiv., 232.

Saponification of the ester with 10% methanolic potassium hydroxide solution gave **2||3-androstan-17α-ol-2,3-diacid**, m. p. 291–293° (uncor.), $[\alpha]^{24}D$ +2.4° (ethanol).

*Anal.* Calcd. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94; neut. equiv., 169.2. Found: C, 67.78; H, 9.06; neut. equiv., 167.

**Dibromination of Androstan-17α-ol-3-one 17-Hexahydrobenzoate (Ia). General Procedure for Polarimetric Determinations.**—The reactions were carried out in dilute solution to avoid precipitation of the 2,2-dibromo derivative IIIa. To a solution of 0.125 g. of the ketone Ia in 15.00 cc. of acetic acid[15] 1.55 cc. of a solution of two moles of bromine in acetic acid was added rapidly from a buret and the mixture was then transferred to a 2-dcm. saccharimeter tube; readings were made as soon as the solution had decolorized sufficiently. A few typical results are given in Fig. 1.

The results with sodium acetate and 30% hydrogen peroxide added to C. P. acetic acid[15] were the same as given below for cholestanone. In the

(7) Jacobsen, THIS JOURNAL, **62**, 1620 (1940). See also Schwenk and Whitman, *ibid.*, **59**, 948 (1937).

(8) Ruzicka, Plattner and Aeschbacher, *Helv. Chim. Acta*, **21**, 866 (1938); Marker, Wittle and Plambeck, THIS JOURNAL, **61**, 1333 (1939).

(9) See Wilds and Djerassi, *ibid.*, **68**, 1715 (1946), for references to earlier work.

(10) Wilds and Djerassi, *ibid.*, **68**, 1712 (1946).

(11) All melting points are corrected unless noted otherwise. All rotations were determined with 5–10 mg. of sample in 1.2 cc. of solvent in a 1-dcm. tube of 1-cc. capacity.

(12) The microanalyses were carried out by Mr. Joseph Alicino, Metuchen, New Jersey, and Mr. George L. Stragand, Microchemical Laboratory, University of Pittsburgh, Pittsburgh, Pa.

(13) For nomenclature, see Sobotka, "Chemistry of the Sterids," Williams and Wilkins Co., Baltimore, Md., 1937.

(14) This structure is based on analogy to known cases; *cf.* Plattner and Fuerst, *Helv. Chim. Acta*, **26**, 2266 (1943).

(15) Baker C. P. glacial acetic acid or Eimer and Amend C. P. Tested Purity Reagent glacial acetic acid was used in all our studies, since their water content (see Table I) was sufficiently low,

case of peroxide, polarimeter readings could not be obtained because the solution was too colored.

**Effect of Water on the Bromination in Acetic Acid.**—For the isolation of the inhibitor formed during the treatment of acetic acid with permanganate, the acid was fractionated through a thirty-plate Todd column and the fractions analyzed for water by means of the Karl Fischer reagent.[16] Addition of known amounts of water to acetic acid–methanol mixtures gave excellent recoveries, thus demonstrating the reliability of this method for acetic acid. The results are summarized in Table I.

TABLE I

EFFECT OF WATER CONTENT OF ACETIC ACID ON DIBROMINATION OF Ia

| Nature of acetic acid | Mg. $H_2O$/10 cc. | Time required for complete dibromination, min. | Half life of rearrangement (ref. 2) |
|---|---|---|---|
| C. P. glacial acetic acid (Baker) | 31 | 7 | 60 min. |
| C. P. glacial acetic acid (Eimer and Amend) | 22 | 5 | 41 min. |
| As above, but fractionated (fractions 2–7) | 14–4 | <5 | 15–17 |
| Fractionated and added 100 mg. of $H_2O$ | | 53 | *ca.* 3 hr. |
| C. P. glacial acetic acid distilled from 5% permanganate[a] | 190–245[b] | 240 | *ca.* 18 hr. |
| As above, but fractionated; | | | |
| Fraction 1 | 426 | *ca.* 8 hr. | [c] |
| Fraction 2 | 29 | 11 | 43 |
| Fraction 3 | 4 | 5 | 15 |

[a] Three liters of distillate was collected from 4 l. of C. P. acetic acid. [b] This value varied, depending on how quickly the distillation was carried out. [c] $[\alpha]^{23}D$ +68° after forty-eight hours.

As was to be expected, the addition of the calculated amount of acetic anhydride to C. P. acetic acid distilled from permanganate and refluxing for about two hours abolished the retarding effect of the water on the bromination and rearrangement.

**2,4-Dibromoandrostan-17α-ol-3-one 17-Hexahydrobenzoate (IVa).**—Before the influence of distillation from oxidizing substances was recognized, the optimum procedure[1] for the preparation of the 2,4-dibromo compound IVa involved isolation and rearrangement of the 2,2-isomer. Based on the results obtained in the above polarimeter reactions, the following direct procedure has given good results. A warm solution of 2 g. of the ketone Ia in 25 cc. of C. P. glacial acetic acid was treated with 24.8 cc. of a solution of 1.59 g. of bromine in C. P. acetic acid. Decolorization was very rapid and after adding 2 cc. of 4 *N* hydrogen bromide solution, the flask was stoppered, allowed to stand at room temperature for two and one-half hours, and the crystals of the 2,4-dibromo derivative IVa were filtered. Further quantities were obtained on diluting the filtrate and recrystallizing from ethanol–chloroform; the total yield of satisfactory material of m. p. 164–165°,[17] $[\alpha]^{23}D$ −6.5°, was 85–90%.

**Rearrangement of the 2,2-Isomer IIIa without Added Hydrogen Bromide.**—Wilds and Djerassi[1] noted that the recrystallization of the 2,2-dibromo compound from acetic acid, reported by Inhoffen and Zuehlsdorff,[3] actually resulted in rearrangement to the 2,4-isomer IVa. Further study has yielded the following results, all of which were obtained with 100 mg. of compound in 1 to 2 cc. of solvent: (1) When warmed quickly and immediately cooled, the 2,2-isomer crystallized out and practically no rearrangement occurred. (2) When warmed for three minutes or longer and the solution cooled for several hours at 10°, up to 80% of the pure 2,4-isomer IVa could be isolated. (3) It was found that rearrangement occurred during the short heating period, rather than afterward, because when a sample was transferred to the polarimeter tube after heating for eight minutes, the rotation was 27° and did not change after twenty-four hours. (4) The addition of 10 mg. of anhydrous sodium acetate or one drop of 30% hydrogen peroxide solution completely prevented the rearrangement, even when heated for ten minutes. However, when added after the short heating period of three to five minutes, the yield of 2,4-isomer was 80%. Water had no effect in preventing this rearrangement when heated. Shaking a suspension of IIIa in C. P. glacial acetic acid for one-hundred and twenty hours at room temperature with or without the addition of acetate or peroxide gave quantitative recovery of the 2,2-isomer.[18]

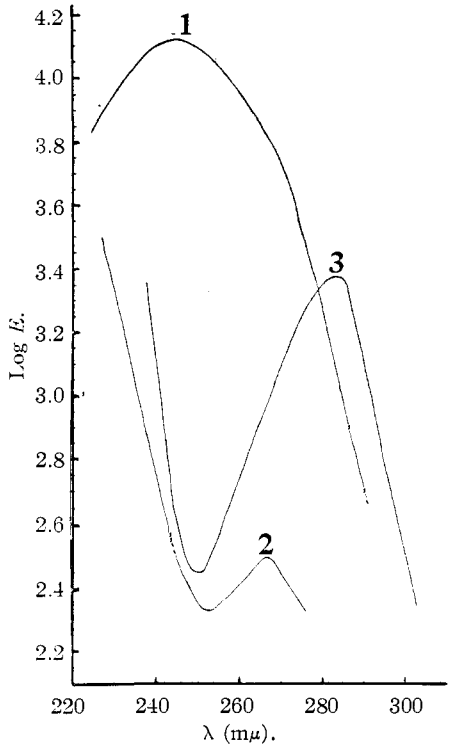



Fig. 2.—Ultraviolet absorption spectra (in 95% ethanol): curve 1, compound IXd; curve 2, compound X; curve 3, compound XI.

**Rearrangement of Δ¹,2-Bromoandrosten-17α-ol-3-one 17-Hexahydrobenzoate (VIIa).**—A solution of 150 mg. of the unsaturated bromo compound VIIa[1,3,19] in 5 cc. of redistilled C. P. glacial acetic acid and 0.5 cc. of 4 *N* hydrogen bromide solution was allowed to stand at room temperature for twenty-three hours and then diluted with water. The gummy product was isolated by ether extraction, washed with alkali and water, dried and evapo-

(16) Smith, Bryant and Mitchell, THIS JOURNAL, **61**, 2407 (1939).

(17) The melting points of either the 2,2- or 2,4-isomer were found by us to be of little value, regardless of the rate of heating or immersion of the capillary just below their melting points. For the 2,2-isomer IIIa, melting points (with decomposition) ranging from 152–154° to 185–186° have been observed, while for the 2,4-isomer IVa, we have encountered values ranging from 153–154° to 175–176°. The best criterion was the rotation ($[\alpha]D$ +110° for IIIa and −6° for IVa), which could be determined in either chloroform or acetic acid, since the values were identical in both solvents.

(18) The experiments at room temperature were carried out with 100 mg. of 2,2-dibromo compound and 15 cc. of acetic acid, since the compound was only slightly soluble in acetic acid at room temperature.

(19) Prepared in 35% yield by heating IIIa with collidine for fifteen minutes and chromatographing the product.

rated. The oil (found: Br, 17.95) on treatment with methanol gave an amorphous solid, m. p. 47–65°, $[\alpha]^{23}D$ +10.8° (chloroform), which showed a maximum at 234 mμ, log $E$ = 3.92.[20] This shift in absorption from 255 mμ (starting material VIIa) to the neighborhood of 231 mμ (absorption of compounds of type VI) would be in accord with structure VIII. The slightly higher maximum of this impure product probably was due to contamination with some starting material. The structure VIII was further supported by the fact that whereas the bromine in the original compound was resistant to collidine treatment, refluxing of the entire rearrangement product with 0.6 cc. of collidine[21] for fifteen minutes gave 34 mg. (52%) of collidine hydrobromide and chromatography[22] of the dehydrobromination product led to the known 1,4-androstadien-17α-ol-3-one 17-hexahydrobenzoate (IXa),[1,3] in 43% yield (crude product).

**Debromination of Δ¹,2-Bromoandrosten-17α-ol-3-one 17-Hexahydrobenzoate (VIIa).**—The conversion of the Δ¹,2-bromo ketone VIIa to Δ¹-testosterone hexahydrobenzoate (VIa), important for the structure proof of the former,[5] has been carried out in unspecified yield by Inhoffen and Zuehlsdorff[3] by refluxing the bromo ketone VIIa in ethanol with zinc dust for four hours. We recovered most of the starting material under those conditions (possibly due to differences in the zinc dust), but when the reflux time was extended to eighteen hours, 89% of crude VIa was isolated, showing a single maximum at 231.5 mμ, log $E$ = 3.82. Chromatography and recrystallization yielded 57% of Δ¹-testosterone hexahydrobenzoate (VIa), m. p. 159.5–161°, $[\alpha]^{23}D$ +43.7° (chloroform), maximum at 231 mμ, log $E$ = 3.83.

Reduction of VIIa with chromous chloride[22a] gave a nearly quantitative recovery of the starting material and reduction with zinc and acetic acid seemed to result in reduction of the double bond and the bromine atom.

**2-Bromotestosterone Hexahydrobenzoate.**—This compound was needed for comparative purposes with the isomeric Δ¹,4-bromo compound VIIIa, described above.

Refluxing of 1 g. of IVa in 4 cc. of collidine for one and one-half minutes removed 115% of hydrogen bromide (on the basis of collidine hydrobromide isolated), demonstrating the great lability of the bromine atom in the 4-position. Crystallization from hexane gave a 39% yield of 2-bromotestosterone hexahydrobenzoate, m. p. 147.5–148.5° (dec.), $[\alpha]^{22}D$ +91.9° (chloroform), maximum at 244.5 mμ, log $E$ = 4.08. Inhoffen and Zuehlsdorff[3] obtained the compound in unspecified yield and reported m. p. 161–162°.

*Anal.* Calcd. for $C_{26}H_{37}O_3Br$: C, 65.38; H, 7.79; Br, 16.76. Found: C, 65.35; H, 7.84; Br, 17.01.

**Dehydrobromination of 2α-Bromoandrostan-17α-ol-3-one 17-Hexahydrobenzoate[22b] (IIa).**—Bromination of the ketone Ia with either bromine in acetic acid[3] or N-bromosuccinimide in carbon tetrachloride[23] gave the 2α-bromo compound IIa, m. p. 182–183°, $[\alpha]^{23}D$ +42.5° (chloroform) in 52% yield; reported,[3] m. p. 181–182°.

*Anal.* Calcd. for $C_{26}H_{39}O_3Br$: C, 65.11; H, 8.18; Br, 16.69. Found: C, 64.92; H, 8.20; Br, 16.33.

The dehydrobromination was carried out essentially as described by Inhoffen and Zuehlsdorff,[3] except that the product was worked up as described below for Δ¹-cholestenone. Δ¹-Androsten-17α-ol-3-one 17-hexahydrobenzoate (VIa) was obtained in 42% yield, m. p. 161–162°, (lit.[3] 160–161°), $[\alpha]^{23}D$ +45.3° (chloroform), maximum at 231.5 mμ, log $E$ = 3.83. From the later fractions of the chromatogram, testosterone hexahydrobenzoate (Va) was isolated in 18% yield, m. p. 122–124°, (lit.[3] 127°), $[\alpha]^{23}D$ +82.5° (chloroform), maximum at 242 mμ, log $E$ = 4.12.

**Dibromination of Androstan-17α-ol-3-one 17-Acetate (Ib).**—When carried out in a polarimeter tube with C. P. acetic acid as described for the hexahydrobenzoate Ia, the rotation rose to a maximum of $[\alpha]^{23}D$ +111° and dropped within six hours to −8° with a "half-life"[2] of fifty-three minutes ($[\alpha]^{23}D$ + 61°), thus showing, contrary to the statement in the literature,[24] that the rate of rearrangement is the same in both series. On diluting the reaction mixture with water when the rotation reached its highest value and recrystallizing from ethanol, colorless needles of the previously unknown 2,2-dibromo compound IIIb,[25] m. p. 139–140°, $[\alpha]^{23}D$ +106.4° (chloroform), were obtained.

*Anal.* Calcd. for $C_{21}H_{30}O_3Br_2$: C, 51.44; H, 6.17; Br, 32.60. Found: C, 51.47; H, 6.15; Br, 32.27.

Rearrangement of the above product gave the known 2,4-dibromo isomer IVb with m. p. 187–188° (dec.) (lit.[26] 194°), $[\alpha]^{23}D$ −10.9° (chloroform).

### Bromination of Cholestanone

**Dibromination of Cholestanone.** (a) **In the Polarimeter.**—The results were nearly identical with those obtained with the hexahydrobenzoate (Fig. 1) and are therefore not repeated.

(b) **In C. P. Glacial Acetic Acid.**[15]—To obtain 2,2-dibromocholestanone (IIIc) in glacial acetic acid without added substances, it was necessary to carry out the bromination in a more concentrated solution than described previously.[10] When 1 g. of cholestanone in 30 cc. of acetic acid was brominated with a solution of 0.833 g. of bromine in 13 cc. of acetic acid, the flask cooled for thirty minutes and the crystals filtered, as much as 53% of the 2,2-isomer IIIc, m. p. 142–145°, $[\alpha]^{22}D$ +100° (chloroform), was obtained. To obtain consistent results under these conditions, it was essential to cool the mixture immediately after addition of the bromine, since the rearrangement proceeded rather rapidly at room temperature. The undiluted filtrate was allowed to stand for twenty-four hours at room temperature, whereupon *ca.* 30% of the nearly pure 2,4-isomer IVc,[10] m. p. 188–191° (dec.), $[\alpha]^{22}D$ −0.11° (chloroform) had crystallized out.

By the use of glacial acetic acid, distilled from 5% (by weight) of potassium permanganate or chromic trioxide, the rate of decolorization as well as of rearrangement was slowed appreciably and it was possible to obtain consistently 68–71% of the 2,2-isomer IIIc by filtration of the reaction mixture. The analytical sample of 2,2-dibromocholestanone crystallized from ethanol–chloroform as well-formed prismatic needles, m. p. 145–147°, $[\alpha]^{22}D$ +104° (chloroform).[4]

*Anal.* Calcd. for $C_{27}H_{44}OBr_2$: C, 59.56; H, 8.15; Br, 29.36. Found: C, 59.48; H, 8.20; Br, 29.54.

(20) The absorption spectra were determined in a Beckman quartz photoelectric spectrophotometer using spectroscopically pure 95% U. S. P. ethanol. Readings usually were carried out in 2.5 mμ intervals, except in the neighborhood of maxima or minima where readings were carried out every 0.5 mμ. $E = c \log \frac{I_0}{I}$ for a 1-cm. cell, where $c$ is the concentration in moles per liter.

(21) The collidine in all dehydrobrominations was white label Eastman Kodak Co. material and was used without further purification. Recent work has indicated that carefully fractionated collidine gives better results.

(22) The alumina used in all chromatograms was obtained from the Aluminum Company of America, grade F-20, minus 80 mesh.

(22a) Julian, Cole, Magnani and Meyer, THIS JOURNAL, **67**, 1728 (1945).

(22b) Djerassi, *J. Org. Chem.*, in press, presents evidence for the assignment of α and β notations in the 2-bromo-3-keto*allo*steroid series.

(23) Djerassi and Scholz, *Experientia*, **3**, 107 (1947).

(24) Inhoffen and Zuehlsdorf (ref. 3) assumed that the acetate group facilitated the rearrangement and only the 2,4-isomer IVb has been described.

(25) Dannenberg, Dissertation, Danzig, 1937 (publ. 1938), p. 37, obtained a dibromoandrostan-17α-ol-3-one 17-acetate of m. p. 148° in the presence of added hydrogen bromide. This material was probably a mixture of the 2,2- and 2,4-isomers, since we found that mixtures of the two compounds had rather sharp melting points. Thus a sample of m. p. 146–149° had the $[\alpha]^{23}D$ +68.8° and another of m. p. 152–154° showed $[\alpha]^{23}D$ +63°.

(26) Inhoffen, Zuehlsdorff and Huang-Minlon, *Ber.*, **73**, 451 (1940).

The compound was rearranged readily in acetic acid solution in the presence of hydrogen bromide to the known 2,4-dibromocholestanone.[10]

(c) **In the Presence of Sodium Acetate.**—The bromination was carried out as above in glacial acetic acid, but at the end of the bromine addition, 0.63 g. of anhydrous sodium acetate was added immediately. The crystals of the 2,2-dibromo compound appeared within minutes and 71% of the pure 2,2-isomer IIIc, m. p. 145–147°, $[\alpha]^{22}D$ +98° (chloroform) (Found: Br, 29.21) was isolated. The sodium acetate had to be added at the end of the bromination, since, if added before, the reaction did not go to completion at room temperature in a reasonable period of time.

(d) **In the Presence of Hydrogen Peroxide.**—The reaction was carried out as in (c), but sufficient 30% hydrogen peroxide solution was added to remove all of the hydrogen bromide liberated. The yield of 2,2-isomer isolated from the red solution was 62–68%.

**Bromination of 2β-Bromocholestanone**[2b] (IIc).—Wolff[27] reported that the bromination of 2-bromocholestanone in chloroform–acetic acid gave 2,4-dibromocholestanone, m. p. 193–194°, in unspecified yield. When the bromination of 2β-bromocholestanone was carried out in acetic acid and sodium acetate added at the end of the reaction, 46% of 2,2-dibromocholestanone (IIIc) was obtained. Similar results were observed with N-bromosuccinimide in the presence of strong light.[23]

**Δ¹,2-Bromocholesten-3-one (VIIc).**—One gram of 2,2-dibromocholestanone was refluxed for ten minutes with 4 cc. of collidine,[21] the product chromatographed over alumina,[22] and most of the crystalline fractions investigated spectrophotometrically. The yield of solid of m. p. 86–90° and showing a maximum at 256 mμ was 0.26–0.34 g. (30.5–39.5%). The analytical sample of the Δ¹,2-bromo compound VIIc crystallized in plates from methanol, with the following constants: m. p. 91.5–92.5°; $[\alpha]^{23}D$ +37.4° (chloroform); maximum at 256 mμ, log $E$ = 3.93.

*Anal.* Calcd. for $C_{27}H_{44}OBr$: C, 69.83; H, 9.55; Br, 17.24. Found: C, 69.60; H, 9.44; Br, 17.15.

**Dehydrobromination of 2β-Bromocholestanone**[22b] (IIc).—2β-Bromocholestanone, obtained by any one of three methods,[23,28,29] crystallized as long needles from ethanol chloroform, m. p. 167.5–168°, $[\alpha]D$ +40.8° (chloroform).

A solution of 1.5 g. of pure 2β-bromocholestanone in 6 cc. of collidine was refluxed for one hour, which removed 91–95% of the bromine on the basis of collidine hydrobromide isolated. After working up as usual,[10] the residue which crystallized spontaneously, was purified by adsorption on alumina and elution in about twenty fractions with solvents ranging from petroleum ether (b. p. 30–60°)–benzene (9:1) to pure benzene. Every third fraction was analyzed for absorption in the ultraviolet. From the first fractions, about 37–44% of Δ¹-cholestenone (VIc), m. p. 89–93°, max. at 231–233 mμ was obtained; 13–28% of material in the intermediate fractions showed maxima at 235–238 mμ; and 12–23% of Δ⁴-cholestenone (Vc), m. p. 72–75°, $[\alpha]^{24}D$ +81.2° (chloroform), max. at 243 mμ was isolated from the last fractions. The analytical sample of Δ¹-cholestenone (VIc) crystallized from dilute ethanol as glistening blades, m. p. 98–100°, $[\alpha]^{23}D$ +57.5° (chloroform), $[\alpha]D$ +62.6° (ethanol), max. at 231 mμ, log $E$ = 3.99. Butenandt, *et al.*,[6] reported m. p. 95°, $[\alpha]D$ +64.5 (ethanol), while Jacobsen[7] obtained the compound in poor yield as a hydrate, m. p. 107–108°, $[\alpha]D$ +65° (ethanol). No evidence of hydrate formation could be observed, even in samples that were dried at room temperature only and no cholestanone, presumably arising from debromination,[7] was isolated under these conditions.

(27) Wolff, Dissertation, Danzig, 1937 (publ. 1938), p. 14; *cf.* Butenandt, Schramm, Wolff and Kudszus, *Ber.*, **69**, 2779 (1936). However, Ralls (ref. 4) seemed to have obtained IIIc from IIc with iodine monobromide.

(28) Butenandt and Wolff, *Ber.*, **68**, 2091 (1935).

(29) Djerassi and Scholz, THIS JOURNAL, in press.

*Anal.* Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.38. Found: C, 84.37; H, 11.52.

**Bromination of Methyl 3-Keto*allo*etiocholanate (Id)**

**Methyl 3-Keto*allo*etiocholanate (Id).**—Two grams of methyl 3-hydroxy*allo*etiocholanate[30,31] (m. p. 174–175°, $[\alpha]^{23}D$ +52.2° (chloroform), was oxidized in 60 cc. of glacial acetic acid with 0.6 g. of chromic trioxide. The yield of satisfactory ketone Id of m. p. 179–181° was 81–87%; the purified sample had m. p. 181–182°, $[\alpha]^{22}D$ +71.8 (chloroform). Further amounts of the ketone could be isolated from the mother liquors *via* the semicarbazone[32] and cleavage of the latter in dioxane with 43% sulfuric acid.

On raising the amount of chromic trioxide to that employed by Steiger and Reichstein,[30] nearly 50% of methyl 2||3-*allo*etiocholan-2,3-diacid-17-carboxylate[13] of m. p. 194–196°, $[\alpha]^{25}D$ +50.8° (chloroform), was obtained.

*Anal.* Calcd. for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48; methoxyl, 8.16; neut. equiv., 190.2. Found: C, 66.42; H, 8.39; methoxyl, 8.63; neut. equiv., 192.2.

Saponification with potassium hydroxide gave colorless hexagonal plates of the tribasic acid (iso*allo*etiolithobilianic acid) with m. p. 274–276° (uncor.), $[\alpha]^{23}D$ +38.2° (ethanol).

*Anal.* Calcd. for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25; neut. equiv., 122.1. Found: C, 65.49; H, 8.10; neut. equiv., 125.6.

Treatment of the above dibasic or tribasic acids with diazomethane gave the completely esterified methyl iso*allo*etiolithobilianate, m. p. 81–83°, $[\alpha]^{23}D$ +37.5° (chloroform). Plattner and Fuerst[14] isolated this compound in the oxidation of 3-keto*allo*etiocholanic acid and reported m. p. 82–83°, $[\alpha]D$ +47° (chloroform).

*Anal.* Calcd. for $C_{23}H_{36}O_6$: C, 67.67; H, 8.88; methoxyl, 22.80. Found: C, 67.21; H, 8.47; methoxyl, 23.30.

**Methyl 2α-Bromo-3-keto*allo*etiocholanate**[22b] (IId).—Bromination of Id as described for cholestanone[23,28,29] gave 0.44 g. (71%) of the monobromo ketone IId with m. p. 176–180° (dec.). Recrystallization from ethanol yielded needle-like blades with m. p. 186–188° (dec.), $[\alpha]^{23}D$ +78.8° (chloroform).

*Anal.* Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.60; Br, 19.43. Found: C, 61.66; H, 7.40; Br, 19.21.

**Methyl Δ¹,3-Keto*allo*etiocholenate (VId).**—Dehydrobromination was accomplished in 40% yield by refluxing 1 g. of the bromo ketone IId with 4 cc. of collidine for forty-five minutes. After chromatographing and recrystallizing from hexane–acetone, the colorless needles melted at 192–193.5°, $[\alpha]^{23}D$ +92.6° (chloroform), maximum at 232 mμ, log $E$ = 3.79.

*Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.24; H, 9.06.

**Dibromination of Methyl 3-Keto*allo*etiocholanate (Id).**

(a) **Methyl 2,2-Dibromo-3-keto*allo*etiocholanate (IIId).**—When the dibromination of the ketone Id was investigated in the polarimeter in the usual manner, the rotation of the solution rose to a maximum of +167° at the point of decolorization and dropped within a few hours to +50°. However, if the solution was diluted with water when it had reached the highest reading and filtered after a few minutes, the product melted at 65–92°, solidified at 124° and melted at 172–174° with decomposition, $[\alpha]^{23}D$ +135.7° (chloroform). The rotation did not rise on recrystallization and no explanation of the difference of the two rotations, which has been observed several times, can be given. The compound did not lose weight on drying for six hours at 130° and 1 mm. and the rotation of the compound was nearly the same in acetic acid as in chloroform, thus excluding the possibility of solvent of crystallization. Conversion of the compound to the cor-

(30) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1040 (1938).

(31) Sorkin and Reichstein, *ibid.*, **29**, 1209 (1946).

(32) v. Euw and Reichstein, *ibid.*, **27**, 1851 (1944).

responding $\Delta^1$,2-bromo derivative VIId showed that it had predominantly the 2,2-dibromo structure.

*Anal.* Calcd. for $C_{21}H_{30}O_3Br_2$: C, 51.44; H, 6.17; Br, 32.60. Found: C, 51.90; H, 6.36; Br, 32.38.

(b) **Methyl 2,4-Dibromo-3-keto*allo*etiocholanate (IVd).**—A solution of 5 g. of the ketone Id in 100 cc. of C. P. glacial acetic acid was treated with a solution of 4.84 g. of bromine in 75.6 cc. of acetic acid followed by 10 drops of 4 *N* hydrogen bromide solution. Rosets of needles started to appear after one hour and after standing overnight at room temperature, they were collected and washed well with water; yield, 5.7 g. (77%), m. p. 193–195° (dec.), $[\alpha]^{24}D$ +26° (chloroform). Dilution of the filtrate yielded an additional 16–19% of satisfactory material. The analytical sample crystallized from ethanol as long needles, m. p. 199–200° (dec.), when immersed in the bath at 170°, $[\alpha]^{23}D$ +24.2° (chloroform).

*Anal.* Calcd. for $C_{21}H_{30}O_3Br_2$: C, 51.44; H, 6.17; Br, 32.60. Found: C, 51.02; H, 6.13; Br, 32.61.

**Methyl $\Delta^1$,2-Bromo-3-keto*allo*etiocholenate (VIId).**—Dehydrobromination of the 2,2-dibromo derivative IIId was carried out in the usual manner and on chromatographing yielded 36% of material showing a maximum at 253–256 mμ. Less than 10% of the product exhibited a maximum at 247 mμ (corresponding to the 1,4-dienone) showing that only a small amount, if any, of 2,4-dibromo isomer could have been present in the original sample. The analytical sample was obtained from hexane–acetone as rosets of thin needles, m. p. 168–170°, $[\alpha]^{23}D$ +77.9° (chloroform), max. at 256.5 mμ, log $E$ = 3.85.

*Anal.* Calcd. for $C_{21}H_{29}O_3Br$: C, 61.61; H, 7.14; Br, 19.52; methoxyl, 7.58. Found: C, 61.97; H, 7.42; Br, 19.63; methoxyl, 7.91.

**Methyl $\Delta^4$,2-Bromo-3-ketoetiocholenate.**—Short treatment of the 2,4-dibromo compound IVd with collidine as described for the corresponding androstane compound IVa gave colorless needles (45%) from hexane–acetone with m. p. 162.5–163.5° (dec.), $[\alpha]^{23}D$ +147.2° (chloroform), maximum at 243.5 mμ, log $E$ = 4.04.

*Anal.* Calcd. for $C_{21}H_{29}O_3Br$: C, 61.61; H, 7.14; Br, 19.52; methoxyl, 7.58. Found: C, 61.86; H, 7.11; Br, 18.98; methoxyl, 7.37.

Debromination of the above compound with chromous chloride in acetone[22a] gave 93% of crude (m. p. 110–116°) methyl $\Delta^4$,3-ketoetiocholenate (Vd). Recrystallization from hexane raised the m. p. to 128–130°, $[\alpha]^{23}D$ +145.6° (chloroform), maximum at 242 mμ, log $E$ = 4.16, (lit.,[32] m. p. 131–132°, $[\alpha]^{15}D$ +144.7° (acetone).

**Methyl 3-Ketoetiochola-1,4-dienate (IXd).**—A solution of 6.98 g. of the 2,4-dibromo compound IVd (unrecrystallized, as obtained in (b) above) in 27.5 cc. of collidine[21] was refluxed for seventy minutes and the crude crystalline product purified by chromatography and recrystallization from hexane–acetone; yield 2.22 g. (45% over-all yield based on the ketone Id), m. p. 151–153°. Further recrystallization raised the melting point of the colorless prismatic needles to 155.5–156°, $[\alpha]^{23}D$ +82.8° (chloroform), maximum at 244.5 mμ, log $E$ = 4.12.

*Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; methoxyl, 9.45. Found: C, 76.86; H, 8.44; methoxyl, 9.10.

Spectrophotometric analysis of the various chromatogram fractions gave no evidence of the presence of the 4,6-isomer (maximum at 284 mμ) in contrast to the results observed in the other series (IXa,[1] IXb,[3] IXc,[10]).

**Methyl 3-Acetoxy-1-methyl-1,3,5-estratriene-17-carboxylate (X).**—The dienone phenol rearrangement[9] was carried out on 1 g. of the above dienone (m. p. 151–153°) in 20 cc. of acetic anhydride and 330 mg. of concentrated sulfuric acid. Treatment with water gave 1.02 g. (90%) of the acetate with m. p. 94.5–97°, $[\alpha]^{24}D$ +195.6 (chloroform). Recrystallization from ethanol produced three forms of the acetate: m. p. 91–93°, $[\alpha]^{23}D$ +198.1° (chloroform), m. p. 127.5–128°, $[\alpha]^{23}D$ +197.8° (chloroform) and m. p. 133–135°, $[\alpha]^{23}D$ +200.3° (chloroform). The absorption spectrum, shown in Fig. 2, exhibited the characteristic shift[33] of the maximum of a phenol acetate to lower wave length and lower extinction as compared to that of the phenol; maximum at 266.5 mμ, log $E$ = 2.49, and minimum at 252 mμ, log $E$ = 2.33.

*Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found (m. p. 91–93°): C, 74.04; H, 8.27; (m. p. 127.5–128°): C, 74.76; H, 8.15; (m. p. 133–135°): C, 74.27; H, 7.96.

**3-Hydroxy-1-methyl-1,3,5-estratriene-17-carboxylic Acid (XI).**—Saponification of 0.5 g. of the acetate X by refluxing with 25 cc. of 10% methanolic potassium hydroxide solution yielded 0.38 g. (90%) of the acid XI, m. p. 131–136°, solidifying at 168° and melting at 209–211° (dec.), $[\alpha]^{23}D$ +181.6° (chloroform). The analytical sample, m. p. 223–225° (dec.), $[\alpha]^{23}D$ +194.4° (chloroform), was obtained from hexane–acetone. The absorption spectrum shown in Fig. 2, exhibited a maximum at 283 mμ, log $E$ = 3.37, and a minimum at 250 mμ, log $E$ = 2.45.

*Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; neut. equiv., 314.5. Found: C, 76.29; H, 8.34; neut. equiv., 324.

## Summary

The use of acetic acid, distilled from permanganate or chromic trioxide, in the dibromination of some 3-ketosteroids of the *allo* series has been shown to retard both the formation and the rearrangement of the 2,2-dibromo ketones III to the 2,4-isomers IV, as compared with C. P. acetic acid. This effect has been shown to be due to the formation of appreciable amounts of water. The bromination process has been followed polarimetrically and procedures have been developed for the preparation of various 2,2-dibromo compounds.

A number of transformations of the mono and di-bromo ketones have been described and it has been shown that in the collidine dehydrobromination of 2-bromo-3-ketosteroids, appreciable amounts of the $\Delta^4$-3-ketone in addition to the $\Delta^1$-isomer are formed.

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(33) John, *Z. physiol. Chem.*, **250**, 11 (1937).