Dehydrogenation of Δ^6-Dehydroestrone to Equilenin (VI).—A solution of 2.5 g. of Δ^6-dehydroestrone acetate in 70 cc. of glacial acetic acid was refluxed with 0.43 g. of freshly sublimed selenium dioxide for ten to fifteen minutes in a current of nitrogen. After filtration of selenium and pouring into water, there was obtained 2.4 g. of crude **equilenin acetate** with a reddish color, which was removed on filtration in hexane–benzene (5:1) solution through a short column of alumina. Recrystallization from methanol gave long prisms, with a slight pink tinge, m. p. 156–157° (cor.), $[\alpha]^{20}D$ +72°; no depression was observed on admixture with the acetate (m. p. 157–158°) prepared from the natural hormone. The ultraviolet absorption spectrum is shown in Fig. 2.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 77.90; H, 6.54. Found: C, 78.16; H, 6.23.

Saponification of the acetate by boiling with 5% methanolic potassium hydroxide solution for twenty-five minutes, followed by sublimation *in vacuo* and recrystallization from dilute ethanol, yielded **equilenin** (VI), m. p. 256–258° (red melt), $[\alpha]^{20}D$ +86.4° (dioxane); the m. p. was undepressed on mixing with a sample of the natural hormone (kindly supplied by Ayerst, McKenna and Harrison, Ltd.). The characteristic spectrum is given in Fig. 2 with maxima at 230, 270, 280, 292, 328 and 340 mμ and was nearly indistinguishable from that of the natural hormone.[15]

(15) Our log E values, for both the natural and semi-synthetic sample, were about 0.2 unit lower than those reported earlier (ref. 11) and the last maximum was observed at 340 mμ (in agreement with Dirscherl and Hanusch, *Z. physiol. Chem.*, **233**, 13 (1935)) rather than at 345 mμ (ref. 11). Our values were obtained on a Beckman Spectrophotometer which had been calibrated both in regard to wave length (benzene) and extinction (potassium chromate in alkali) by the procedure of Hogness, *et al.*, *J. Phys. Chem.*, **41**, 379 (1937).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.89; H, 6.75.

Summary

The Wohl–Ziegler bromination of $\Delta^{1,4}$-androstadiene-3,17-dione (and of the corresponding 17-acetoxy derivative) proceeds smoothly and after dehydrobromination of the intermediate 6-bromo compound IIa leads to $\Delta^{1,4,6}$-androstatriene-3,17-dione (IIIa). Aromatization in mineral oil solution of IIIa at 600° results in the formation of Δ^6-dehydroestrone (Δ^6-isoequilin) (IV) in 40% yield, whose structure was proved by hydrogenation to estrone (V) and by dehydrogenation to equilenin (VI). This constitutes the first partial synthesis of equilenin from a steroid with an angular methyl group at C-10.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. VII.[1] Contribution to the Bromination of Δ^4-3-Ketosteroids and a New Partial Synthesis of the Natural Estrogens

BY CARL DJERASSI, G. ROSENKRANZ, J. ROMO, ST. KAUFMANN AND J. PATAKI

$\Delta^{1,4}$-Dien-3-ones (XI) of the steroid series represent the key intermediates in the partial synthesis of the female sex hormones, estrone and estradiol from non-aromatic steroids possessing an angular methyl group at C-10, since thermal treatment results in aromatization of ring A with formation of the desired phenol (XIV).[2,3] This process is now used commercially and the required dienones have so far only been prepared by dibromination of saturated 3-keto*allo*steroids followed by dehydrobromination of the resulting 2,4-dibromo derivatives. The alternate approach involving as a starting material a Δ^4-3-ketosteroid (I), such as testosterone, appeared attractive and was studied in very considerable detail by Inhoffen[2] and by Butenandt.[4] Their study was limited to a model Δ^4-3-ketosteroid, Δ^4-cholesten-3-one (Ic) and was concerned primarily with the behavior of this ketone toward bromine. These reactions, which at times proved to be very involved, led these workers[2,4] to the conclusion that mono- and poly-bromination (up to *eight* moles of bromine) of Δ^4-3-ketosteroids (I) results in substitution at C-4 and in ring B and that, therefore, these ketones are useless as starting materials for the partial synthesis of the estrogens. Since a reinvestigation of this problem in this laboratory has provided a novel partial synthesis of all of the major natural estrogens and has thus thrown open to question the structure assignments of a considerable number of compounds,[2,4] a detailed discussion of the bromination of Δ^4-3-ketosteroids (I) is necessary.

At the outset it should be noted that most of the work done on the bromination of Δ^4-3-ketosteroids (I) was carried out in acetic acid, alone or diluted with another solvent, and the present discussion is limited to this type of solvent. It is stated[2,4,5] that *monobromination* of Δ^4-cholesten-3-one (Ic) in ether–acetic acid leads to the 6-bromo derivative (IIc). This substance (m. p. 132°, u. v. maximum at 248 mμ) is known and has been prepared by a number of methods[5,6] but *it has never been isolated* in the monobromination of Δ^4-cholesten-3-one (Ic) in acetic acid, because a difficultly separable mixture is formed,[7] and there-

(1) Paper VI, Kaufmann, Pataki, Rosenkranz, Romo and Djerassi, THIS JOURNAL, **72**, 4531 (1950).

(2) *Cf.* Inhoffen, *Angew. Chem.*, **53**, 473 (1940); *ibid.*, **59**, 207 (1947).

(3) (a) Hershberg, Rubin and Schwenk, *J. Org. Chem.*, **15**, 292 (1950); (b) Wilds and Djerassi, THIS JOURNAL, **68**, 2125 (1946); Djerassi and Scholz, *ibid.*, **71**, 3962 (1949).

(4) Butenandt, Schramm and Kudsus, *Ann.*, **531**, 176 (1937).

(5) Inhoffen, *Ber.*, **69**, 2141 (1936).

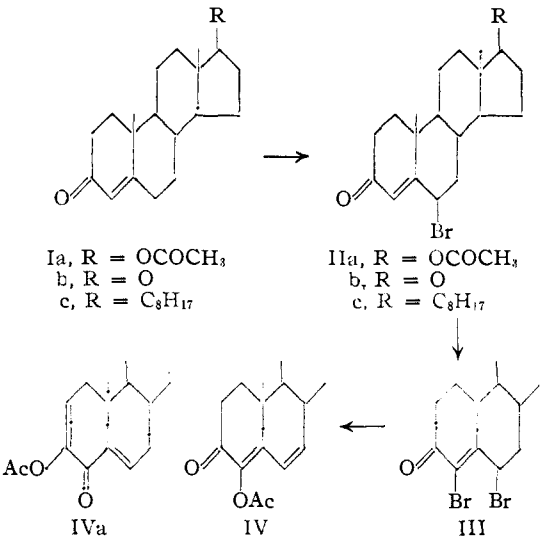
(6) Ruzicka, Bosshard, Fischer and Wirz, *Helv. Chim. Acta*, **19**, 1147 (1936); Dane, Wang and Schulte, *Z. physiol. Chem.*, **245**, 80 (1936); Reich and Lardon, *Helv. Chim. Acta*, **29**, 671 (1946); Martens, *Ann.*, **563**, 131 (1949).

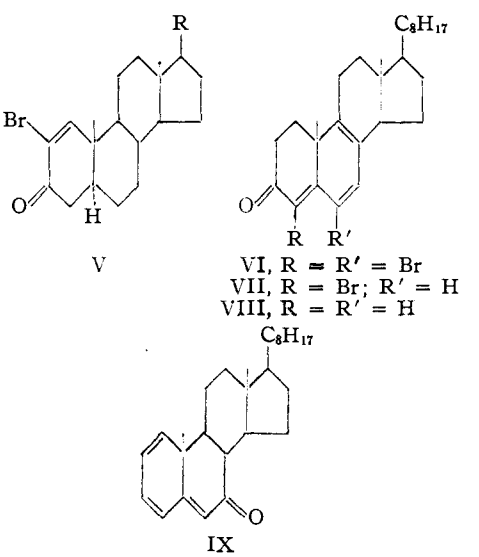
(7) Unpublished observation; *cf.* also ref. 5, p. 2145.

fore, although possible, it is not proved that the 6-bromo derivative II is the initial product in that reaction.[2,4,5] *Dibromination* of Δ^4-cholesten-3-one in ether–acetic acid leads to a homogeneous product,[5,8] m. p. 163°, u. v. maximum at 248 mμ, to which the 4,6-dibromo-Δ^4-cholesten-3-one (III) structure was ascribed.[4,5] The structure proof is based primarily on a series of reactions,[5,9] *none of which* exclude rearrangement of a bromine atom situated originally at C-2. Finally, it is noteworthy that the introduction of a bromine atom on the double bond (III) results in *no change in the spectrum* (as compared to II) and that the dibromo ketone III reacts *readily*[9] with potassium acetate to yield an unsaturated enol acetate, originally (and most likely incorrectly) formulated by Inhoffen[9] as IV, and more recently by Fieser, *et al.*,[9a] as 3-acetoxy-$\Delta^{2,5}$-cholestadien-4-one (IVa).

In marked contrast to these observations is the behavior of Δ^1-2-bromocholesten-3-one and other Δ^1-2-bromo-3-ketosteroids (V), whose structure has been established beyond doubt[10,11] and which proved to be extremely resistant toward potassium acetate.[11] In that instance, the introduction of the bromine atom on the double bond resulted in a bathochromic shift of *ca.* 25 mμ. The obvious conclusion must be drawn that the course of the dibromination of Δ^4-3-ketosteroids (I) in general, and of Δ^4-cholesten-3-one (Ic) in particular, in acetic acid–ether has by no means been established.

The further bromination with up to eight moles of bromine was carried out in Butenandt's laboratory[4,12] and need not be discussed in detail except to point out that structure VI (or its 8–14 double bond isomer) was proposed for this polybromination product. VI as well as its catalytically partially debrominated derivative VII[12] were characterized by ultraviolet absorption maxima at *ca.* 270 mμ, 295 mμ and one below 240 mμ which was not measured. Further removal of bromine[12] afforded an impure trienone, m. p. 76–80°, believed to be VIII, which also showed these three characteristic peaks in the ultraviolet. It is noteworthy that $\Delta^{1,3,5}$-cholestatrien-7-one (IX), whose synthesis seems unambiguous,[13] exhibits maxima at 230 and 350 mμ.[13] In that basis, the ultraviolet absorption spectra of compounds VI–VIII appear to be incompatible with the structures assigned to them and this uncertainty is applicable, *ipso facto*, to their various precursors.[4]





The above mentioned inconsistencies led us to reinvestigate the dibromination of Δ^4-3-ketosteroids, particularly of the androstane series, as a route to the partial synthesis of the estrogens. When carried out in acetic acid–ether solution, testosterone acetate (Ia) afforded a dibromo derivative in 85 to 90% yield on treatment with two moles of bromine at 0°. This substance, m. p. 174° (dec.), $[\alpha]_D$ +43°, u. v. maximum at 248–250 mμ was also obtained on dibromination with

(8) An isomer, m. p. 122° was obtained from the mother liquors and was believed to be a C-6 diastereoisomer, because it afforded the same product with potassium acetate as did the m. p. 163° isomer. Since no spectral data are given for this isomer, the point cannot be decided definitely, but the same situation may obtain as described in the experimental portion of this paper with testosterone acetate.

(9) Inhoffen, *Ber.*, **69**, 1702 (1936).

(9a) Fieser, Fieser and Rajagopalan, *J. Org. Chem.*, **13**, 800 (1948), suggested this alternate structure (IVa) for the enol acetate as arising by a "special mechanism" from Inhoffen's 4,6-dibromo-Δ^4-cholesten-3-one (III) through initial rearrangement to a hypothetical Δ^5-4,4-dibromo-3-ketosteroid. Their alternate structure (IVa), though much more likely than IV, has not been proved unequivocally and has no direct bearing on the structure assignment of the dibromination product(s) of Δ^4-3-ketosteroids (I) (*vide infra*), since regardless of the structure of such bromoketones, a rearrangement must be involved in the enol acetate formation (Fieser, *et al.*) and this rearrangement can of course occur equally well with any one of the four possible dibromination structures Xa-Xd.

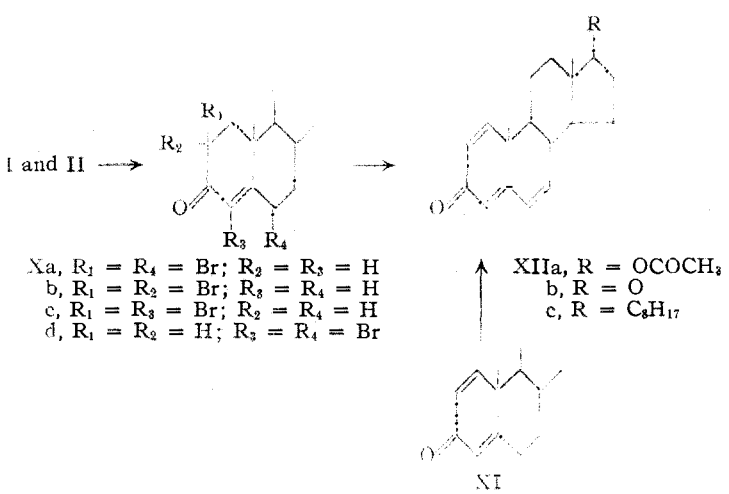
(10) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947); for a discussion of absorption spectra, see p. 2405, footnote 5, and Djerassi and Scholz, *ibid.*, **70**, 1911 (1948).

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

(12) Werner Barkow, D. Sc. Dissertation, Danzig, 1938 (published 1940).

(13) Karrer and Naik, *Helv. Chim. Acta*, **32**, 2392 (1949).

two moles of N-bromosuccinimide in carbon tetrachloride and on monobromination of 6-bromotestosterone acetate (IIa)[14] with bromine in ether–acetic acid. Short boiling with collidine resulted in a smooth loss of *two moles* of hydrogen bromide and afforded in 45% over-all yield (based on Ia) $\Delta^{1,4,6}$-androstatrien-17-ol-3-one 17-acetate (XII), identical with a specimen prepared by an unequivocal method,[1] which involved N-bromosuccinimide bromination of the corresponding $\Delta^{1,4}$-dienone (XIa) followed by collidine dehydrobromination. Occasionally in the dibromination of testosterone acetate (Ia) a dibromo derivative was obtained with the same decomposition point and approximately the same rotation as mentioned above but with an ultraviolet maximum at *ca.* 240 mμ. The same material was also obtained from the mother liquors of the 250 mμ product, but both substances afforded the $\Delta^{1,4,6}$-trien-3-one XIIa in essentially the same yield on dehydrobromination.



Xa, $R_1 = R_4 = Br$; $R_2 = R_3 = H$
b, $R_1 = R_2 = Br$; $R_3 = R_4 = H$
c, $R_1 = R_3 = Br$; $R_2 = R_4 = H$
d, $R_1 = R_2 = H$; $R_3 = R_4 = Br$

Before turning to a consideration of the structure of these bromination products, it will be necessary to discuss two other examples. Δ^4-Androstene-3,17-dione (Ib) also was smoothly dibrominated under the above mentioned conditions to lead in 80% yield to a dibromo ketone, exhibiting a maximum at 240 mμ, which was readily dehydrobrominated to the known $\Delta^{1,4,6}$-androstatriene-3,17-dione (XIIb).[1] 2-Bromo-[15] and 6-bromo-Δ^4-androstene-3,17-dione on monobromination gave an isomeric dibromo ketone, characterized by a maximum at 250 mμ, which similarly yielded the trienone XIIb on collidine dehydrobromination. Finally, the dibromo-Δ^4-cholesten-3-one of Inhoffen[5] was treated with collidine and also afforded $\Delta^{1,4,6}$-cholestatrien-3-one (XIIc). All three trienones (XIIa,b,c) were characterized by three maxima at 222, 256 and 298 mμ. While in this respect the results coincide in the testosterone (Ia), Δ^4-androstene-3,17-dione (Ib) and Δ^4-cholesten-3-one (Ic) series, they differ in that 6-bromo-Δ^4-androstene-3,17-dione (IIb), prepared from Δ^4-androstene-3,17-dione (Ib) and N-bromosuccinimide, possesses a maximum at 240 mμ, in contrast to that at 248 mμ exhibited by the corresponding 6-bromo derivatives (IIa and IIc) of testosterone acetate and Δ^4-cholesten-3-one. The structure of all these 6-bromo derivatives was confirmed by conversion to the $\Delta^{4,6}$-dien-3-ones with their characteristic ultraviolet absorption maxima at 282 mμ; the alternate 2-bromo-Δ^4-androstene-3,17-dione[15] structure was eliminated since under identical conditions it afforded the $\Delta^{1,4}$-dien-3-one (XI, R = O) with its maximum at 244 mμ. This apparently anomalous spectral behavior of 6-bromo-Δ^4-androstene-3,17-dione (IIb) now finds a reasonable explanation in the light of Barton and Miller's observation[15a] that 6α-bromo-Δ^4-cholesten-3-one possesses a maximum at 238 mμ in contrast to the maximum at 248 mμ observed by Inhoffen[5] for the 6β-bromo isomer. This would indicate that the configuration of the 6-bromine atom may have an unexpectedly large influence on the absorption spectrum. The supposition that 6-bromotestosterone acetate (IIa) possesses the 6β configuration and 6-bromo-Δ^4-androstene-3,17-dione (IIb) the 6α configuration is further confirmed by a calculation of the molecular rotation differences.[15b] It is thus seen that spectral data of unsaturated brominated ketosteroids have to be interpreted with caution, particularly since the maximum of a simple 4-bromo-Δ^4-3-ketosteroid is not known.[16]

The above outlined considerations—(a) production of two isomeric dibromo-Δ^4-3-ketosteroids (maxima at 240 or 250 mμ) by either *di*bromination of a Δ^4-3-ketosteroid or *mono*bromination of a 2-bromo- or 6-bromo-Δ^4-3-ketosteroid, (b) the dehydrobromination of either isomeric dibromoketone to the same $\Delta^{1,4,6}$-trien-3-one (XII), and (c) the spectral data—*are most compatible with the expression Xa, i. e., a 2,6-dibromo-Δ^4-3-ketosteroid as the product of the dibromination of Δ^4-3-ketosteroids*. The formation of two isomers with different ultraviolet maxima is readily explained by as-

(14) Meystre and Wettstein, *Exper.*, **2**, 408 (1946).
(15) Djerassi and Scholz, *J. Org. Chem.*, **13**, 697 (1948).

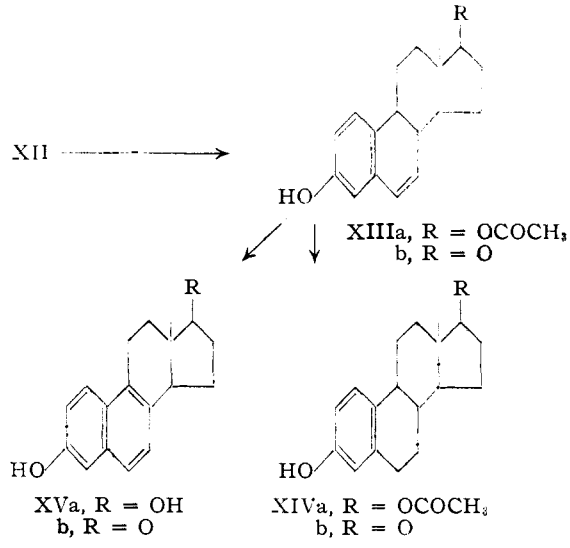
(15a) Barton and Miller, THIS JOURNAL, **72**, 1066 (1950).
(15b) According to Barton and Miller (ref. 15a) Δ[M]D for a 6α-bromine atom is −112, and −329 for the 6β-bromo isomer. Similar calculations demonstrate that the rotatory contribution of the bromine atom in 6-bromotestosterone acetate (IIa) is −365, while that of 6-bromo-Δ^4-androstene-3,17-dione (IIb) amounts to −140.
(16) By analogy to the 2-bromo-Δ^1-3-ketosteroids (V, refs. 10 and 11) a maximum at *ca.* 265 mμ might be predicted. The maximum at 248 mμ reported by Fieser (Fieser and Fieser "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, p. 196) and by Woodward (THIS JOURNAL, **63**, 1123 (1941)) for a so-called 4-bromo-Δ^4-cholesten-3-one was obtained from Dannenberg (*Abhandl. Preuss. Akad. Wiss. Math.-nat. Klasse No. 21* (1939)), who quotes Barkow (ref. 12). An inspection of the latter paper demonstrates clearly that the compound was impure and possessed an unknown constitution.

suming that they are isomeric at C-6.[15a] Structure Xb, a 2,2-dibromo-Δ^4-3-ketosteroid can at the present time not be excluded for the 240 mμ product, since migration of bromine atoms *from* position 2 during collidine dehydrobromination, ultimately yielding a 6-7 double bond are well known.[3b,11,17] Formula Xc, easily accommodated on the basis of chemical evidence is accorded third choice in the absence of definite information on the ultraviolet spectrum of a 4-bromo-Δ^4-3-ketone.[16] Inhoffen and Butenandt's[2,4] structure Xd is the least likely one for either the 240 or the 250 mμ isomer because of the ultraviolet absorption spectrum[16] and the dehydrobromination to the trienone XII; it should be noted that hypothetical rearrangement products could be postulated in that case also to explain the formation of the trienones XII on collidine treatment, but they appear unlikely since until now *no rearrangement of a bromine atom (or a double bond arising from it) to position C-2 is known in the steroid series.*

The striking triple maxima in the ultraviolet absorption spectra of the $\Delta^{1,4,6}$-trien-3-ones XII closely parallel the absorption spectra found by Butenandt[4,12] in some of the *polybrominated* cholestenone derivatives and indicate that these compounds most likely possess such a *$\Delta^{1,4,6}$-trien-3-one structure with one or more bromine atoms on the double bonds*, rather than the $\Delta^{4,6,8}$-trien-3-one structure previously assigned to them.

The synthesis of $\Delta^{1,4,6}$-trien-3-ones (XII) in rather good over-all yield by a two-step process from Δ^4-3-ketosteroids (I) has permitted the partial synthesis of all of the major naturally occurring estrogens. Since Δ^4-3-ketosteroids (I) are readily obtained from both Δ^5-3-hydroxysteroids and from saturated members of the *normal* series (bile acids, pregnanes, certain sapogenins), it is now *possible to synthesize the female sex hormones from every class of steroid.*[18] The synthesis of Δ^6-dehydroestrone (XIIIb), estrone (XIVb) and equilenin (XVb) from $\Delta^{1,4,6}$-androstatriene-3,17-dione (XIIb) has already been recorded in the preceding paper,[1] and the same reaction, *i.e.*, vapor phase aromatization of $\Delta^{1,4,6}$-androstatrien-17-ol-3-one 17-acetate (XIIa) in mineral oil solution at 600° afforded the unknown Δ^6-dehydroestradiol 17-acetate (XIIIa), which on saponification gave Δ^6-dehydroestradiol (XIII, R = OH). This substance exhibited approximately three to five times the biological potency of estrone in rats and on hydrogenation (of the 17-acetate) gave estradiol-17-monoacetate (XIVa) in 87% yield. This represents not only a satisfactory partial synthesis of estradiol but also a useful method for preparing 17-monoesters of estradiol, which have previously been obtained[19] only on careful partial saponification of the corresponding 3,17-diesters. The very strongly negative rotation of the Δ^6-dehydroestrogens (XIII) has already been commented upon[20] and should prove a useful tool for characterization in the eventual isolation of such compounds from natural sources such as urine.

Application of the selenium dioxide procedure[1] to Δ^6-dehydroestradiol (XIII) 3,17-diacetate yielded 17-dihydroequilenin 3,17-diacetate (m. p. 126°) and on saponification 17-dihydroequilenin (XVa) (m. p. 241°), which proved to be identical with the lithium aluminum hydride reduction product of natural equilenin (XVb). Since our product has thus been correlated in its configuration at C-17 with estradiol (XIV, R = OH) and testosterone (I, R = OH), it must possess the 17-β configuration and thus confirms unequivocally the structure of 17-"α"-dihydroequilenin[21] of Marker.



(17) Wilds and Djerassi, THIS JOURNAL, **68**, 1712 (1946).

(18) Inhoffen and Stoeck, *Exper.*, **4**, 426 (1948), unsuccessfully attempted to employ a 3-keto*normal*steroid (coprostanone) as starting material.

(19) Miescher and Scholz, *Helv. Chim. Acta*, **20**, 263 (1937).

(20) Rosenkranz, Djerassi, Kaufmann, Pataki and Romo, *Nature*, **165**, 814 (1950). This remarkably large effect on the rotation of the steroid by the introduction of a 6-7 double bond (which directly does not affect any asymmetric carbon atom) must be due to resulting distortion of the valency angles of the adjacent asymmetric center C-8 and quite likely also of C-9, C-13, C-14 and C-17.

(21) Marker, THIS JOURNAL, **60**, 1897 (1938). Marker's "α" is a trivial index relating his compound (correctly) to "α"-estradiol. The actual configuration at C-17 is β, in conformance with the newer nomenclature (Fieser and Fieser, "Natural Products Related to Phenanthrene"). The nomenclature employed in Elsevier's "Encyclopedia of Organic Chemistry," Amsterdam, 1946, Vol. 14, p. 98, is definitely misleading since it refers to the "natural" 17-dihydroequilenin as 17-*epi*dihydroequilenin in order to differentiate it from the 17-α isomer isolated by Wintersteiner, *et al.*, THIS JOURNAL, **58**, 2652 (1936); *ibid.*, **59**, 765 (1937). In view of our correlation with estradiol and testosterone, it is suggested that the use of trivial indeces and prefixes be dropped and that 17-α and β be employed in the sense advanced by the Fiesers (ref. 16). Thus the isomer described in this paper should be referred to as 17-dihydroequilenin-17β. It should be noted that through a mistake, the biological activities of the isomers as reported by Marker were reversed in the Fieser monograph (ref. 16, p. 327) and this coupled by the "abnormal" melting point behavior (the β-isomer is higher melting than Wintersteiner's product) has led to an incorrect assignment of configurations in Fieser's book.

Experimental[22,23]

6-Bromotestosterone Acetate (IIa).—Contrary to earlier reports[14] an excess of N-bromosuccinimide was not found to be advantageous. Equimolar quantities of N-bromosuccinimide and testosterone acetate were refluxed in the absence of light in carbon tetrachloride solution for twenty to thirty minutes whereupon all the reagent had been consumed. Filtration, evaporation of the solvent and trituration with hexane gave 72% of 6-bromotestosterone acetate, which after recrystallization from hexane–ether showed the following constants: m. p. 140–142° (127–130° dec. Kofler), $[\alpha]^{20}D$ −16°, u. v. maximum at 248 mμ (log *E* 4.19).

Anal. Calcd. for $C_{21}H_{29}O_3Br$: C, 61.59; H, 7.13. Found: C, 61.86; H, 7.37.

To confirm the structure of the compound, it was dehydrobrominated with collidine (30 minutes of refluxing) to yield $\Delta^{4,6}$-androstadien-17-ol-3-one 17-acetate, m. p. 143–144°, $[\alpha]^{20}D$ + 36°, u. v. maximum at 284 mμ (log *E* 4.53). Saponification gave $\Delta^{4,6}$-androstadien-17-ol-3-one, m. p. 204–205°, $[\alpha]^{20}D$ +76.6°, maximum at 284 mμ (log *E* 4.47).[24]

6-Bromo-Δ^4-androstene-3,17-dione (IIb).—The reaction was carried out as above using Δ^4-androstene-3,17-dione (Ib) and led to the corresponding 6-bromo derivative in 67% yield, m. p. 175–177° (dec., cor.), $[\alpha]^{20}D$ +108°, u. v. maximum at 240 mμ (log *E* 4.23); reported[25] m. p. 171°.

Anal. Calcd. for $C_{19}H_{25}O_2Br$: C, 62.47; H, 6.90; Br, 21.87. Found: C, 62.61; H, 6.99; Br, 21.79.

The structure proof, necessary because of the unusually low position of the u. v. maximum, was provided by collidine dehydrobromination (91% yield of collidine hydrobromide) which gave 51% of pure $\Delta^{4,6}$-androstadiene-3,17-dione, m. p. 168–170° (Kofler), $[\alpha]^{20}D$ +138°, maximum at 282 mμ (log *E* 4.52); reported[25] m. p. 173°. The identical procedure with 2-bromo-Δ^4-androstene-3,17-dione[15] yielded 55% of $\Delta^{1,4}$-androstadiene-3,17-dione (XI, R = O)[15] with m. p. 135–138°, u. v. maximum at 244 mμ (log *E* 4.23).

Dibromination of Testosterone Acetate (Ia): A. With Bromine in Ether–Acetic Acid.—A solution of 19.85 g. of testosterone acetate in 650 cc. of dry ether was cooled in ice, a few drops of 4 *N* hydrogen bromide in acetic acid was added followed by a solution of 19.5 g. of bromine in 180 cc. of acetic acid at the rate at which the solution decolorized. After *ca.* five to ten minutes, the ether and part of the acetic acid was distilled under reduced pressure at 15–20° and the product was filtered and washed with ethanol. The yield of colorless needles was usually *ca.* 65–70% with decomposition point varying from 168–170° to 172–174° and rotations between $[\alpha]^{20}D$ +43 to 47°. Without being able to determine the reason, the maximum was either at 240 mμ (log *E* 4.10) or at 250 mμ (log *E* 4.11). From the filtrate by dilution with water and recrystallization 20–25% of additional material was isolated with the same m. p., rotations varying from +37 to +43° and u. v. maximum invariably at 240 mμ (log *E* 4.10). This experiment has been repeated ten times by three investigators with the same results. Recrystallization from ethanol–chloroform gave the analytical sample with m. p. 172–174° (dec.), although occasionally a m. p. of 155–158° (dec.), 140° (Kofler) was observed, $[\alpha]^{20}D$ +46°, u. v. maximum as above.

Anal. Calcd. for $C_{21}H_{28}O_3Br_2$: C, 51.65; H, 5.78. Found (for two samples with different u. v. maxima): C, 51.78, 51.89; H, 5.64, 5.60.

B. With N-Bromosuccinimide in Carbon Tetrachloride.—A mixture of 3.3 g. of testosterone acetate, 3.5 g. of N-bromosuccinimide and 50 cc. of carbon tetrachloride was refluxed for twenty-five minutes with exposure to strong light. After the usual work-up and recrystallization from chloroform–ethanol there was obtained 1.0 g. (20%) of the dibromo derivative, m. p. 165–168° (dec.), $[\alpha]^{20}D$ +44°, u. v. maximum at 248 mμ (log *E* 4.15). This specimen was dehydrobrominated separately with collidine and yielded 50% of the trienolone acetate XIIa.

Monobromination of 6-Bromotestosterone Acetate (IIa).—Monobromination of 6-bromotestosterone acetate in ether–acetic acid afforded in 60% yield the dibromo derivative with m. p. 169–173° (dec.), $[\alpha]^{20}D$ +42°, u. v. maximum at 248 mμ (log *E* 4.10), (Br, calcd.: 32.74; found: 33.03). Dehydrobromination similarly led to the trienolone acetate XIIa.

Dibromination of Δ^4-Androstene-3,17-dione (Ib).—The dibromination was carried out exactly as described for testosterone acetate except that a *suspension* of Δ^4-androstene-3,17-dione (Ib) was employed since the ketone was not sufficiently soluble in ether. Occasionally, decolorization was very slow and a red, unstable intermediate formed, which suddenly dissolved with decolorization and vigorous evolution of hydrogen bromide. Usually, decolorization was rapid, the solid simultaneously going into solution, and it is conceivable that impurities in the ether play a role in this reaction. On working up as above, *ca.* 60% of colorless crystals, m. p. 170–173°, $[\alpha]^{20}D$ +112°, u. v. maximum at 240 mμ was obtained and an additional 20–22% of equal purity from the mother liquors. Recrystallization from chloroform–ethanol yielded colorless needles, m. p. 172–175° (dec.), 157–160° (Kofler), $[\alpha]^{20}D$ +116°, u. v. maximum at 240 mμ (log *E* 4.19). Identical results were obtained in four experiments.

Anal. Calcd. for $C_{19}H_{24}O_2Br_2$: C, 51.37; H, 5.45; Br, 35.98. Found: C, 51.09; H, 5.69; Br, 35.99.

Monobromination of 2-Bromo- and 6-Bromo-Δ^4-androstene-3,17-dione.—The monobromination of the 2-bromo[15] and 6-bromo (IIb, *vide supra*) isomers had to be carried out in a suspension of 2 g. of ketone in 70 cc. of ether and 25 cc. of glacial acetic acid in view of their insolubility, which was also responsible for the fact that complete decolorization and solution required nearly forty minutes. Larger amounts of acetic acid accelerated the reaction markedly, but also lowered the yield. The identical dibromo ketone was obtained in each instance in *ca.* 60% yield, m. p. 161–163° (dec., Kofler); $[\alpha]^{20}D$ +107°, u. v. maximum at 250 mμ (log *E* 4.20), found: C, 51.05; H, 5.27. Dehydrobromination in the usual manner (see below) produced $\Delta^{1,4,6}$-androstatriene-3,17-dione (XIIb).

$\Delta^{1,4,6}$-Androstatrien-17-ol-3-one 17-Acetate (XIIa).—A solution of 22.4 g. of dibromotestosterone acetate in 120 cc. of dry, distilled collidine was refluxed for thirty minutes, which resulted in the loss of two moles of hydrogen bromide (18.5 g., 95% yield of collidine hydrobromide). After the usual work-up, concentration of the ether extract yielded light tan crystals, m. p. 144–147°. Together with a small amount of product isolated by chromatographing the mother liquors, the total yield ranged between 50 to 60%, with an average of 45% over-all yield based on testosterone acetate (Ia) in nine separate experiments. The yield was not influenced whether dibromo ketone with u. v. maximum at 240 or 250 mμ was employed. The analytical sample crystallized as large, prismatic needles from ether or hexane–acetone with m. p. 151–153° (Kofler), $[\alpha]^{20}D$ −11°, u. v. maxima (Fig. 1) at 222 mμ (log *E* 4.18), 256 mμ (log *E* 4.09) and 298 mμ (log *E* 4.21). No depression in m. p. was observed on

(22) Melting points, marked Kofler, were determined on the Kofler block and are corrected; all others were carried out in capillaries and are uncorrected unless noted otherwise. Rotations were determined on *ca.* 60–100 mg. of substance in chloroform solution (unless indicated otherwise) in a 2-dem. tube of 10-cc. capacity. Ultraviolet absorption spectra were measured in 95% ethanol solution with a Beckman Quartz Photoelectric Spectrophotometer.

(23) The microanalyses were carried out in our Microanalytical Department under the direction of Srta. Amparo Barba. The Srtas. Paquita Revaque and Ann Rochman were responsible for all spectra and rotations.

(24) Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940), reported m. p. 209–211° for the alcohol and m. p. 143–144° for the acetate; Inhoffen (ref. 11) gives m. p. 202° and 144°, respectively.

(25) Ruzicka, *et al.*, *Helv. Chim. Acta*, **19**, 1147 (1936); **20**, 328 (1937).

admixture with material prepared by an unequivocal method[1] and the two specimens proved to be identical in all other respects. For analysis, a sample was sublimed at 0.002 mm.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.47; H, 8.16.

$\Delta^{1,4,6}$-Androstatrien-17-ol-3-one (XII, R = OH).—Two grams of the above acetate was saponified by refluxing with 2 g. of potassium hydroxide in 80 cc. of methanol and 10 cc. of water. Dilution with water, filtration and recrystallization from ether–hexane afforded 1.7 g. of the alcohol, m. p. 156–157.5° (Kofler), $[\alpha]^{20}D$ +17.6°, u. v. maxima at 222 mμ (log *E* 4.17), 258 mμ (log *E* 4.23) and 298 mμ (log *E* 4.16).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.26; H, 8.58.

$\Delta^{1,4,6}$-Androstatriene-3,17-dione (XIIb).—The collidine dehydrobromination of dibromo-Δ^4-androstene-3,17-dione was carried out exactly as described for the corresponding 17-acetoxy derivative and yielded 45% of $\Delta^{1,4,6}$-androstatriene-3,17-dione (XIIb) with m. p. 164–165°, $[\alpha]^{20}D$ +82°, +71° (dioxane), u. v. maxima at 222, 256 and 298 mμ which agreed in every respect with the sample prepared by the alternate procedure.[1]

$\Delta^{1,4,6}$-Cholestatrien-3-one (XIIc).—Collidine dehydrobromination of dibromo-Δ^4-cholesten-3-one[8] (m. p. 162–163°, $[\alpha]^{20}D$ +52°, u. v. maximum at 250 mμ (log *E* 4.08). *Anal.* Calcd. for $C_{27}H_{42}OBr_2$: Br, 29.48. Found: Br, 29.82) in the above manner afforded 60% of crude $\Delta^{1,4,6}$-cholestatrien-3-one. The substance was very soluble, but could be recrystallized from petroleum ether (b. p. 30–60°) at Dry Ice temperature; m. p. 82–83°, $[\alpha]^{20}D$ 0°, u. v. maxima at 224 mμ (log *E* 4.03), 258 mμ (log *E* 3.97) and 300 mμ (log *E* 4.11).

Anal. Calcd. for $C_{27}H_{40}O$: C, 85.20; H, 10.59. Found: C, 85.05; H, 10.75.

A somewhat impure cholestatrienone (m. p. 76–80°, $[\alpha]D$ −17°, u. v. maxima at below 230 mμ, *ca.* 265 mμ and *ca.* 290 mμ) obtained by Barkow[12] by catalytic reduction of a dibromo compound believed to be VI may very likely be identical with our product. Attempts by Martens[6] to prepare this trienone by another method led only to an oil.[26]

Δ^6-Dehydroestradiol 17-Monoacetate (XIIIa).—A solution of 9 g. of the trienolone acetate XIIa in 900 cc. of mineral oil was aromatized at 600° as described for the corresponding 17-ketone[1] and after filtration of the chilled condensate and washing with hexane gave 4.5 g. (52%) of crude phenol with m. p. 210–230°. Recrystallization from methanol afforded *ca.* 40% of nearly colorless crystals of m. p. 245–249°. The analytical sample of the **17-monoacetate** after repeated recrystallization and sublimation *in vacuo* showed m. p. 250–252° (Kofler), $[\alpha]^{20}D$ −203°, u. v. maxima (Fig. 1) at 222 mμ (log *E* 4.46), 262 mμ (log *E* 3.93) and 302 mμ (log *E* 3.47).

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.96; H, 7.47.

Acetylation of the above 17-monoacetate in the usual manner with pyridine–acetic anhydride yielded **Δ^6-dehydroestradiol 3,17-diacetate** as shiny blades from methanol with m. p. 153.5–155° (Kofler), $[\alpha]^{20}D$ −162°, u. v. maximum at 264 mμ (log *E* 4.01).

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.74; H, 7.03.

Saponification of the 17-monoacetate afforded **Δ^6-dehydroestradiol** (XIII, R = OH) as prisms from dilute methanol with m. p. 225–226° (Kofler), undepressed on admixture with a specimen prepared[1] by lithium aluminum hydride reduction of Δ^6-dehydroestrone (XIIIb); $[\alpha]^{20}D$ −171°, u. v. maxima at 262 mμ (log *E* 4.00) and 302 mμ (log *E* 3.47); for estrogenic activity, see discussion.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.07; H, 8.36.

(26) See however Romo, Djerassi and Rosenkranz, *J. Org. Chem.*, **15**, 896 (1950).

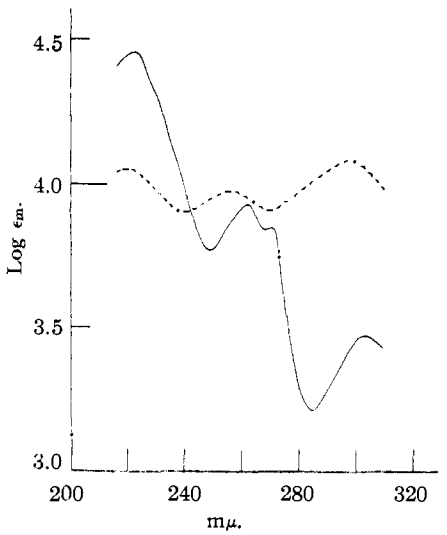


Fig. 1.—Ultraviolet absorption spectra (in 95% ethanol solution): ++++ $\Delta^{1,4,6}$-androstatrien-17-ol-3-one 17-acetate (XIIa); —— Δ^6-dehydroestradiol 17-monoacetate (XIIIa).

Hydrogenation of Δ^6-Dehydroestradiol to Estradiol (XIV, R = OH).—A solution of 1.14 g. of Δ^6-dehydroestradiol 17-monoacetate (XIIIa) in 100 cc. of ethyl acetate was shaken with 50 mg. of 10% palladium-on-charcoal (American Platinum Works) for one-half hour under hydrogen. Filtration, evaporation and recrystallization from methanol gave 1.0 g. (87%) of **estradiol 17-monoacetate** (XIVa) as prisms with m. p. 217–219° (Kofler), $[\alpha]^{20}D$ +47°, u. v. maximum at 280 mμ (log *E* 3.42) and minimum at 250 mμ (log *E* 3.03); only the m. p. of this ester (without analysis) was reported,[19] 215–217.5°.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 76.40; H, 8.34. Found: C, 76.76; H, 8.25.

Saponification with alkali afforded **estradiol** (XIV, R = OH) with m. p. 176–177°, undepressed on admixture with authentic hormone, $[\alpha]^{20}D$ +80.4° (dioxane), u. v. maximum at 280 mμ (log *E* 3.33) and minimum at 250 mμ (log *E* 2.41).

For further characterization, **estradiol 3,17-diacetate** was prepared, m. p. and mixed m. p. 127–129° (Kofler), $[\alpha]^{20}D$ +45°, u. v. maxima at 266 mμ (log *E* 2.84) and 274 (log *E* 2.81) and minima at 248 mμ (log *E* 2.54) and 272 mμ (log *E* 2.75).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.18; H, 8.04.

17-Dihydroequilenin-17β (XVa). A. By Lithium Aluminum Hydride Reduction of Equilenin (XVb).[27]—Natural equilenin (kindly donated by Ayerst, McKenna and Harrison) was converted to the acetate, m. p. 156–158°, and the latter (0.4 g.) in 30 cc. of tetrahydrofuran (dried over potassium hydroxide followed by calcium chloride and distillation) was refluxed with 0.8 g. of lithium aluminum hydride in tetrahydrofuran for fifteen minutes. After the usual work-up, 17-dihydroequilenin-17β (XVa) was crystallized from hexane–acetone whereupon it showed m. p. 246–248° (capillary), 240–241° (Kofler), $[\alpha]^{20}D$ +60° (dioxane), u. v. maxima (Fig. 2) at exactly the same points observed recently[1] for equilenin (XVb): lit.[21] m. p. 248°, no rotation given.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.39; H, 7.61.

(27) NOTE ADDED IN PROOF: Bachmann and Dreiding, THIS JOURNAL, **72**, 1323 (1950), recorded the lithium aluminum hydride reduction of equilenin methyl ether and came to the same conclusion regarding the configuration of the C-17 hydroxyl group of 17-dihydroequilenin as expressed in the present article (ref. 21).

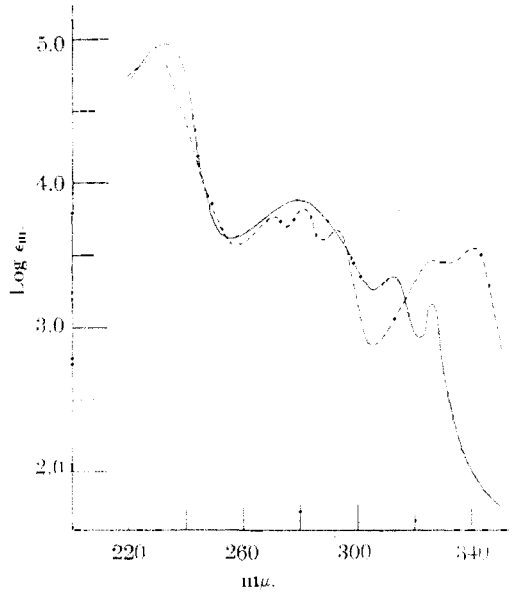


Fig. 2.—Ultraviolet absorption spectra: ——— 17-dihydroequilenin-17β (XVa); - - - 17-dihydroequilenin-17β 3,17-diacetate.

Acetylation produced **17-dihydroequilenin-17β 3,17-diacetate** with m. p. 124–126° (Kofler), $[\alpha]^{20}D$ −12°, u. v. spectrum Fig. 2; reported,[21] m. p. 124°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 75.19; H, 7.04.

B. By Selenium Dioxide Dehydrogenation of Δ⁶-Dehydroestradiol 3,17-Diacetate.—Dehydrogenation of 1 g. of diacetate with 156 mg. of freshly sublimed selenium dioxide in 15 cc. of boiling acetic acid for eight minutes produced 0.81 g. of 17-dihydroequilenin-17β 3,17-diacetate with m. p. 115–118°. Recrystallization from ether-hexane raised the m. p. to 125–127° (Kofler), $[\alpha]^{20}D$ −15°. No depression of the m. p. was observed on mixing with the sample prepared by method A and the ultraviolet absorption spectra proved to be identical.

Alkaline saponification afforded 17-dihydroequilenin-17β with m. p. 246–248° (capillary), undepressed on admixture with a specimen prepared according to method A, $[\alpha]^{20}D$ + 56° (dioxane). The ultraviolet absorption spectrum was practically identical with that depicted in Fig. 2 for material prepared by procedure A.

Summary

A recapitulation of the earlier work of Inhoffen and Butenandt on the bromination of Δ⁴-3-ketosteroids (I), which had led to the conclusion that these ketones could not be employed for the partial synthesis of the estrogens, has demonstrated several inconsistencies. The reinvestigation of the dibromination in ether–acetic acid solution of Δ⁴-3-ketosteroids (I), in particular of the androstane series, has shown that the resulting dibromo derivatives on collidine dehydrobromination produce Δ¹,⁴,⁶-trien-3-ones (XII) in satisfactory overall yield. On the basis of these results, several alternate structures are proposed for the intermediate dibromo compounds, taking into consideration their marked tendency toward rearrangement and their ultraviolet absorption spectra.

Δ¹,⁴,⁶-Androstadiene-3,17-dione (XIIb), thus obtained, has already[1] been converted into Δ⁶-isoequilin, estrone and equilenin, and its corresponding 17-acetoxy derivative on similar treatment has now led to Δ⁶-dehydroestradiol, estradiol and 17-dihydroequilenin-17β. The stereochemistry of the C-17 isomeric dihydroequilenins is discussed.

The present experiments thus constitute a novel, partial synthesis of all of the major, naturally occurring female sex hormones from the potent male hormones testosterone and Δ⁴-androstene-3,17-dione.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. VIII.[1,2] The Dienone–Phenol Rearrangement in the Steroid Series. Synthesis of a New Class of Estrogens

BY CARL DJERASSI, G. ROSENKRANZ, J. ROMO, J. PATAKI AND ST. KAUFMANN

Partial aromatization of a bicyclic ring system possessing an angular methyl group with concomitant migration of the angular substituent was first observed in the santonin (I) series.[3] This rearrangement can be carried out at or near room temperature in acetic anhydride containing a small amount of acid[4] and furnishes the phenol, desmotroposantonin (II), in high yield. Subsequently, Inhoffen and co-workers[5] applied these reaction conditions to analogous steroidal dienones (III) in the hope of preparing members of the female sex hormone series. The resulting products, though insoluble in alkali, were clearly shown to be phenols, and by analogy to the santonin–desmotroposantonin rearrangement they were assigned the 1-methyl-3-hydroxy-1,3,5-triene structure IV. Thus in the case of Δ¹,⁴-androstadien-17-ol-3-one (IIIa), 1-methylestradiol (IVa) was believed to have been obtained. In spite of the comparative non-specificity of estrogenic activity, exhibited by a variety of substances, this close

(1) Presented in part on the program of the Division of Medicinal Chemistry at the Philadelphia, Pa., meeting of the American Chemical Society, April 11, 1950.

(2) Paper VII, Djerassi, Rosenkranz, Romo, Kaufmann and Pataki, THIS JOURNAL, **72**, 4534 (1950).

(3) Andreocci, *Ber.*, **26**, 1373 (1893); Clemo, Haworth and Walton, *J. Chem. Soc.*, 1110 (1930).

(4) Huang-Minlon, Lo and Cho, THIS JOURNAL, **65**, 1780 (1943).

(5) See Inhoffen, *Angew. Chem.*, **53**, 471 (1940); **59**, 207 (1947); *Lieb. Ann.*, **563**, 127 (1949).