trimethoxyflavone in the same quantities of acetic and hydrobromic acid as in the last experiment was refluxed for 40 min., diluted with water, neutralized, and the resulting precipitate dissolved in aqueous acetic acid (50%, 50 ml.) and extracted with boiling benzene (three 20-ml. portions). The cooled aqueous liquors deposited a solid which, after trituration with boiling benzene and crystallization from aqueous acetic acid, afforded 4',6-dihydroxy-8-methoxyflavone.

(d) **3,6-Dihydroxy-8-methoxyflavone.**—3-Hydroxy-6,8-methoxyflavone (100 mg.) was partially demethylated in boiling acetic (5 ml.) and hydrobromic acids (48% w./w., 40 ml.) during 15 min., the product isolated as before, and dissolved in boiling aqueous acetic acid (50%, 75 ml.). After extraction with boiling petroleum ether (100–120°, three 20-ml. portions), the aqueous liquors were heated with charcoal. The yellow needles obtained on cooling were crystallized from benzene–petroleum ether and then from aqueous ethanol yielding 3,6-dihydroxy-8-methoxyflavone (24 mg.).

The melting points of these compounds were undepressed on admixture with the appropriate authentic specimen obtained from the corresponding isopropoxymethoxyflavone. All four compounds were readily soluble in aqueous sodium hydroxide but only the flavonol gave a ferric coloration (dark brown in ethanol). Analytical data, etc., of these compounds and their acetates, crystallized from ethanol or aqueous ethanol, are summarized in the third sections of Tables II and III.

Deisopropylation of Methoxyisopropoxyflavones.—The following general method of effecting selective cleavage of the isopropyl groups of isopropoxymethoxy compounds was employed. To a solution of the isopropoxymethoxyflavone or -flavonol (150 mg.) in boiling acetic acid (2 ml.), boiling hydrobromic acid (48% w./w., 10 ml.) was added; the mixture was heated for a further 3 min. and poured into water (100 ml.). The resulting solid was collected, washed with water, and freed from starting material either (if a flavone) by dissolving in aqueous sodium hydroxide and extracting uncleaved ethers with benzene or (if a flavonol) by dissolving in boiling aqueous acetic acid (1:1, 180 ml.) and extracting these with boiling petroleum ether (b.p. 100–120°, three 2-ml. portions). Purification from demethylated compounds was then effected by crystallization from aqueous acetic acid or aqueous methanol. The characteristics of hydroxymethoxyflavones and -flavonols prepared in this way, and of their acetates are listed in the third sections of Tables II and III.

4'-Hydroxy-6,8-dimethoxy- and 3,4'-Dihydroxy-6,8-dimethoxyflavones.—The corresponding 4-benzyl ethers (150 mg.) were dissolved in acetic acid (10 ml.) and concentrated hydrochloric acid (10 ml.), heated in the steam bath for 1 hr., and evaporated *in vacuo*. Crystallization of the residue from aqueous ethanol furnished the 4'-hydroxyflavones; melting points, analytical data, etc., of these compounds and of their acetates are recorded in the third sections of Tables II and III.

Acknowledgment.—The work described in this paper forms a part of the program of the Torry Research Station of the Department of Scientific and Industrial Research.

The Δ^4-Ethylene Ketals of Testosterone and Testosterone Acetate[1]

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Ketalization of testosterone acetate with ethylene glycol by conventional methods with a low concentration of *p*-toluenesulfonic acid catalyst produced a mixture of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate and the well known Δ^5-ketal. Under similar conditions, analogous results were obtained with testosterone. The structures of these new isomeric ketals have been demonstrated by both chemical and physical methods. The Δ^4-ketal of testosterone acetate has been converted by acid catalysis to its Δ^5-isomer.

During the preparation of the ethylene glycol ketal of testosterone acetate (3,3-ethylenedioxyandrost-5-en-17β-ol acetate) as an intermediate for other work, a compound having markedly different physical properties was isolated in fair yield (34%), in addition to the desired product. The analytical data of the new compound were correct for the desired Δ^5-ketal, but the compounds differed in melting point (159–161° *vs.* 202–204° for the known[2] ketal) and in optical rotation (+80.0° *vs.* −52.1° for the known ketal). Neither compound absorbed in the ultraviolet region of the spectrum. A comparison of the infrared spectra showed only minor differences, the most notable of which was the appearance of a weak absorption band at 6.04–6.05 μ in the spectrum[3] of the isomeric compound; a less well defined weak band appeared in the spectrum of the known ketal just below 6.00 μ. These observations led to the tentative conclusion that the isomeric ketal (II, see Fig. 1) possessed a double bond in position 4,5 of the steroid nucleus, in contrast to the 5,6-double bond of the known compound.

Saponification of the acetoxy ketal II led to a hydroxy ketal III which was isomeric with the known Δ^5-ketal[2] of testosterone. Differing physical properties were evident here as with the 17β-acetoxy compounds; there was a different melting point (225–232° *vs.* 185–187° for the known Δ^5-ketal) and a difference in optical rotation (+95.1° *vs.* −45.5° for the Δ^5-isomer). In addition, the infrared spectrum of the new hydroxy ketal displayed a weak absorption band at 6.04 μ in contrast to the 5.98-μ band[3] of the known Δ^5-compound[2] V.

By azeotropic ketalization of testosterone (IV) under similar conditions the Δ^4-ketal of testosterone III was prepared in 30% yield, along with the known Δ^5-ketal V (26% yield). Compound III was identical with that obtained by saponification of the Δ^4-ketal of testosterone acetate and could be converted to the latter by acetylation (see Fig. 1).

Of particular interest were the molar rotational differences between the members of each pair of isomeric compounds.

M_D of Δ^4-17β-Acetoxy ketal II (+300) *minus*	ΔM_D
M_D of Δ^5-17β-Acetoxy ketal VI (−195)	= 495
M_D of Δ^4-17β-Hydroxy ketal III (+320) *minus*	
M_D of Δ^5-17β-Hydroxy ketal V (−151)	= 471

(1) Abstracted in part from the Ph.D. dissertation of J. W. D., Rensselaer Polytechnic Institute, January, 1962.

(2) R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(3) G. Roberts, B. S. Gallagher, and R. N. Jones, "Infrared Absorption Spectra of Steroids," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1958, p. 11. Δ^5-Steroids are reported to absorb in the 5.97–6.00-μ region, and Δ^4-compounds at *ca.* 6.04 μ.

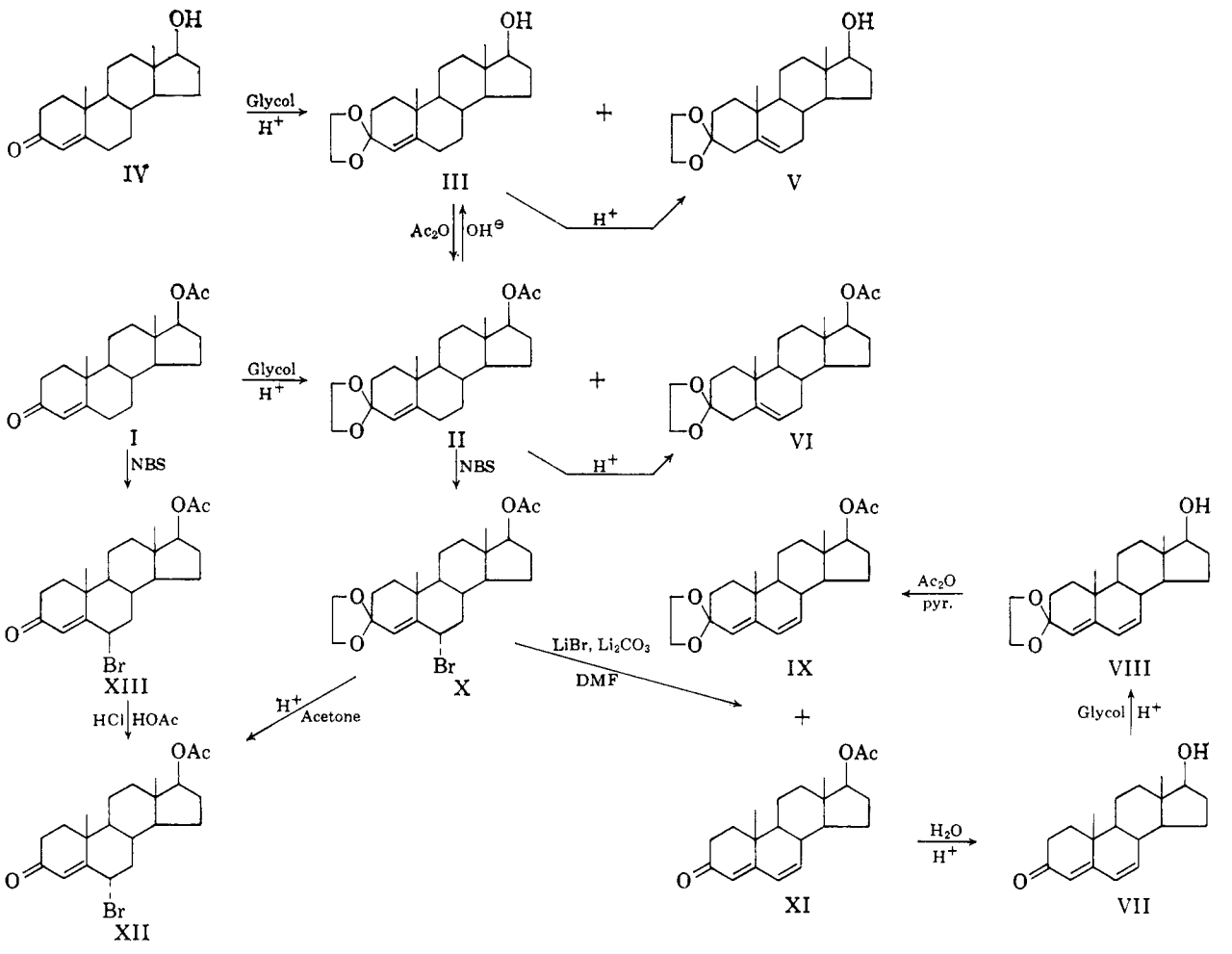

Figure 1

The predicted[4] difference (ΔM_D) between the molar rotations of two isomeric steroids unsaturated between positions 4,5, and 5,6 is 492. This close correlation supported the conclusion that the new steroidal ketals were indeed Δ⁴-isomers of their known Δ⁵-counterparts.

A recent communication[5] reports the preparation and yields of a series of nine steroidal Δ⁴-3-ethylene ketals by substitution of weaker acids (adipic and oxalic) for the *p*-toluenesulfonic acid customarily employed as catalyst. Δ⁴-3-Ketals of testosterone and of 6-dehydrotestosterone (see following) were among those reported; although physical constants and experimental conditions were not described, the broad generality of Δ⁴-3-ketal preparation was amply demonstrated by the wide variety of Δ⁴-3-keto steroids which were similarly ketalized in that study. It is of interest that in most cases Brown, Lenhard, and Bernstein found that adipic acid catalyzed the formation of Δ⁴-ketals only, and that catalysis by the stronger oxalic acid led to the generation of a mixture of Δ⁴- and Δ⁵-ketals; congruently, our products from catalysis with *small* amounts of the much stronger *p*-toluenesulfonic acid were also mixtures of Δ⁴- and Δ⁵- ketals.

Attempts in this laboratory to epoxidize the Δ⁴-ketal in order to establish the location of the double bond in a manner analogous to the scheme of Fernholz and Stavely[6] were unsuccessful. Commercial 40% peracetic acid contains appreciable amounts of mineral acid which hydrolyzed the ketal despite buffering with sodium acetate. Monoperphthalic acid did not effect epoxidation, probably due to steric hindrance by the dioxolane ring to approach of the reagent to the 4,5-double bond.

The structure proof employed by Antonucci, *et al.*,[2] for the Δ⁵-ketal, involving allylic bromination with N-bromosuccinimide, dehydrohalogenation, acid hydrolysis, and identification of the resulting dienone as androsta-5,7-dien-17β-ol-3-one, was then applied. To provide an authentic sample of 3,3-ethylenedioxyandrosta-4,6-dien-17β-ol acetate (IX), the expected product of the application of a similar reaction sequence to the Δ⁴-ketal II, androsta-4,6-dien-17β-ol[7] (VII) was ketalized with glycol and *p*-toluenesulfonic acid by azeotropic distillation in benzene[8] to give 3,3-ethylenedioxyandrosta-4,6-dien-17β-ol (VIII) in 30% yield. Evidence that the 4,6-diene structure was not isomerized during ketalization was provided by the ultraviolet spectrum of VIII, which displayed characteristic[9] ab-

(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 178.

(5) J. J. Brown, R. H. Lenhard, and S. Bernstein, *Experientia*, **18**, 310 (1962).

(6) E. Fernholz and H. E. Stavely, Abstracts of Papers, 102nd National Meeting of the American Chemical Society, 1941, p. 39M.

(7) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4354 (1950).

(8) In an earlier report [S. Bernstein, W. S. Allen, M. Heller, R. H. Lenhard, L. I. Feldman, and R. H. Blank, *J. Org. Chem.*, **24**, 286 (1959)] it was stated that the Δ⁴·⁶-3-keto moiety is unreactive under these conditions. G. J. Fonken, *ibid.*, **26**, 2549 (1961), has, however, described the preparation of the Δ⁴·⁶-3,3-ethylenedioxy derivatives of Δ⁴·⁶-cholestadien-3-one and of Δ⁴·⁶·²²-ergostatrien-3-one by standard methods.

(9) L. Dorfman, *Chem. Rev.*, **53**, 55 (1953).

sorption for the 4,6-dien-3-alkoxy structure at 234, 239, and 248 mμ. Acetylation of VIII then provided the desired 17β-acetoxy compound IX.[10]

Bromination of the Δ⁴-ketal II with N-bromosuccinimide in carbon tetrachloride afforded a monobromo ketal, isolated in 60% yield, whose analysis and infrared spectrum agreed with its formulation (later demonstrated) as 6α-bromo-3,3-ethylenedioxyandrost-4-en-17β-ol acetate (X). When the total crude product from the bromination of II was heated in a boiling solution of 4% *s*-collidine in xylene, only a trace of collidine hydrobromide was produced. When the process was repeated in boiling *s*-collidine, only 38% of the material was dehydrobrominated, based on the collidine hydrobromide isolated; in addition, 52% of the starting bromo ketal was recovered. As an alternative, the dehydrohalogenation conditions of Joly and co-workers[11] were employed. The total crude bromination product of II was heated with lithium bromide and lithium carbonate in dimethylformamide at 100° and the crude product (in 60% yield) was shown by ultraviolet analysis to be a mixture of the 4,6-diene-3-ketal IX (27%) and the 4,6-dien-3-one XI (63%). Hydrolysis of this mixture with dilute methanolic hydrochloric acid afforded a 48% over-all yield of androsta-4,6-dien-17β-ol (VII). The location of the bromine substituent in X was thus shown to be at C-6; consequently, the double bond of the new ketal must be in the 4,5-position.

Cleavage of X under mild conditions, in acetone at room temperature with *p*-toluenesulfonic acid, afforded a bromo ketone XII isomeric with the known[7] 6β-bromotestosterone acetate. The 6α-bromo epimer has not been reported in the literature; however, both its ultraviolet spectrum and optical rotation fall into the pattern established by the properties of other 6-halogenated Δ⁴-3-ones. In a recent summary of the ultraviolet spectra of 6-substituted Δ⁴-3-keto steroids, Ringold and Bowers[12] concluded that 6α-bromo compounds exhibit hypsochromic shifts of 3 to 4 mμ in the ultraviolet compared to the parent Δ⁴-3-ketones and the 6β-bromo epimers show bathochromic shifts of the order of 6 to 8 mμ. Fieser and Fieser[13] have compared the optical rotations of epimeric pairs of 6-chloro- and 6-bromocholestenones. Between these closely analogous compounds, dextrorotatory changes of 45° and 47° are found, respectively, on going from the 6β- to the 6α-epimers. Therefore, the new bromo ketone XII was formulated as 6α-bromotestosterone acetate on the basis of its optical rotation and ultraviolet spectrum. The properties of the two bromo ketones are summarized in Table I.

When 6β-bromotestosterone acetate (XIII) was exposed to the reagents and conditions employed in the acetonolysis of the bromo ketal X, little change in its properties was observed, indicating that little or no epimerization of the 6β-bromine had occurred. Exposure to the epimerization conditions[14] of Bowers and co-workers (hydrogen chloride in glacial acetic acid at room temperature) converted it to 6α-bromotestosterone acetate in good yield.

TABLE I

Compound	M.p.,[a] °C.	$[\alpha]^{25}D$[b]	λ_{max} mμ (ε)[c]
6α-Bromotestosterone acetate (XII)	145–146 (dec.)	+57.6°	237 (13,600)
6β-Bromotestosterone acetate[d] (XIII)	147–148 (dec.)	−13.0°	248 (13,300)
Testosterone acetate (I)	140–142	+96°	241 (16,000)

[a] Uncorrected. [b] In chloroform solution. [c] In ethanol solution. [d] This was a sample prepared in this laboratory by the method of ref. 7, where constants reported were m.p. 140–142°, $[\alpha]^{20}D$ −16°, λ_{max} 248 mμ (ε 15,500).

From the foregoing observation it is inferred that during mild acetonolysis of the bromo ketal X to 6α-bromotestosterone acetate (XII), no epimerization of the bromine substituent at C-6 occurred. Consequently, bromination of the Δ⁴-ketal II with N-bromosuccinimide must have afforded the (equatorial) 6α-bromo ketal directly; in contrast, N-bromosuccinimide bromination of testosterone acetate appears to yield only the (axial) 6β-epimer XIII.

Exposure of the pure bromo ketal X to boiling *s*-collidine for three hours did not effect substantial dehydrohalogenation and 80% of the starting material was recovered. This lack of reactivity is presumably due to the absence of a suitably oriented hydrogen atom on C-7; there is no hydrogen *trans* and coplanar to the equatorial bromine on C-6 to provide the basis for an E2 elimination reaction under the influence of the nucleophile, *s*-collidine.

In a brief series of ketalization experiments with testosterone acetate the concentration of catalyst (*p*-toluenesulfonic acid) was varied, with the other components and the duration (seven hours) held constant. An ultraviolet absorption assay of the crude product was used to determine the extent of reaction. Tripling of the catalyst concentration (from 0.00037 *M* to 0.0011 *M*) was found to increase the yield of total ketals from 49% to 76%. The proportions of Δ⁴- and Δ⁵-isomers produced were not determined in these experiments. Other experiments showed that employment of different quantities of ethylene glycol, which existed as a separate phase during the reaction, as expected had no appreciable effect on the yield.

In preparative experiments with testosterone acetate a 0.0011 *M* catalyst concentration and 0.043 *M* steroid concentration appeared to be optimum for Δ⁴-ketal production. With testosterone, preparation of the Δ⁴-ketal was effected best when both of these concentrations were doubled. In the ketalization of the less reactive androsta-4,6-dien-17β-ol a somewhat higher concentration of catalyst was employed, 0.042 *M* steroid and 0.003 *M* catalyst.

A most interesting observation was that the Δ⁴-ketal II could be converted to its Δ⁵-isomer VI in boiling benzene by a tenth-molar quantity of *p*-toluenesulfonic acid. The crude yield was 45% and no other crystalline product was obtained. Similar results were obtained with the Δ⁴-ketal of testosterone (III). The fact that the use of a low catalyst concentration favors formation of the Δ⁴-ketal, coupled with the demon-

(10) The Δ⁴- and Δ⁴·⁶-ketals were found to be unusually sensitive to hydrolysis; storage in a vacuum desiccator over potassium hydroxide is desirable. Interestingly, the 17β-hydroxy-Δ⁴-ketals were observed to be more resistant to accidental hydrolysis than their acetylated counterparts. Largely for this reason, ketalization of the 17β-hydroxy compound followed by acetylation was found to be more satisfactory for preparative purposes.

(11) R. Joly, J. Warnant, G. Nomine, and D. Berlin, *Bull. soc. chim France*, 366 (1958).

(12) H. J. Ringold and A. Bowers, *Experientia*, **17**, 65 (1961).

(13) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 291.

(14) A. Bowers, E. Denot, M. B. Sanchez, and H. J. Ringold, *Tetrahedron*, **7**, 153 (1959).

strated isomerization of the ketal to its Δ⁵-isomer under what are essentially the usual conditions for the preparation of the Δ⁵-ketal, has led to the hypothesis that the Δ⁴-compound is an intermediate in the formation of the Δ⁵-product usually isolated.

The mechanism of formation of the unsaturated ketals is still uncertain. Brown, Lenhard, and Bernstein[5] advanced a reasonable explanation for the formation of both the α,β- and β,γ-unsaturated compounds through 1,2-addition of the hydroxyl function to either of the intermediate dienol ethers A or B, respectively (see Fig. 2).

An alternative explanation may be advanced, based partly on Djerassi and Gorman's mechanism.[15] The precursor of the Δ²,⁴-enol ether A can be represented as E (see Fig. 2). Displacement, rather than elimination at this point, would lead to the protonated ketal F.[16] Simple loss of a proton would give C, the Δ⁴-ketal. Deprotonation by attack of a base on an allylic proton at C-6 (represented by G) would afford B and then D, the Δ⁵-ketal, by 1,2-addition. This alternative course leading to the Δ⁵-ketal may well be greatly assisted by the presence of larger amounts of catalyst. The scheme outlined also provides a rationale for the demonstrated isomerization of the Δ⁴-ketal structure to its Δ⁵-isomer; by reprotonation of the Δ⁴-ketal, the intermediate F is formed, which can then lose a proton by the alternate path leading eventually to the Δ⁵-ketal D. Further experimentation will be necessary to verify these speculations.

Experimental

Melting points were determined in capillaries and are uncorrected. Ultraviolet spectra were measured with solutions in ethanol and infrared spectra were determined with potassium bromide pellets (1% by weight). Optical rotations were measured with 1% solutions in chloroform.

3,3-Ethylenedioxyandrost-4-en-17β-ol Acetate (II).—Testosterone acetate (I, 5.0 g., 16 mmoles, m.p. 140–142°) was ketalized by azeotropic distillation[2] for 4 hr. in 375 ml. benzene with 80 mg. (0.42 mmole) of *p*-toluenesulfonic acid monohydrate and 23 ml. of ethylene glycol. Recrystallization of the crude solid product from a mixture of acetone and methanol afforded 1.91 g. of needle like crystals of the Δ⁴-ketal II, m.p. 152–155° (33.7%). The compound showed strong ether absorption (10.55 μ) and acetate carbonyl absorption (5.78 μ) in the infrared, plus a weak band at 6.04 μ attributed to the 4,5-double bond. An analytical sample, prepared by several recrystallizations from *n*-hexane containing a trace of pyridine, had m.p. 159–161°, $[\alpha]^{25}D$ +80.0°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.69; H, 9.30.

Concentration of the recrystallization liquors led to the crystallization of 2.0 g. (35.3%) of the known Δ⁵-isomer VI, m.p. 202–204°, $[\alpha]^{25}D$ −51°; lit.[2] m.p. 203–205°, $[\alpha]^{29}D$ −52.1°.

Saponification of 3,3-Ethylenedioxyandrost-4-en-17β-ol Acetate (II).—Saponification of II (1.00 g., 2.67 mmoles) in refluxing aqueous ethanolic potassium hydroxide for 1 hr. afforded 0.90 g. of 3,3-ethylenedioxyandrost-4-en-17β-ol (III), m.p. 218–229°. Two recrystallizations from acetone containing a trace of pyridine gave the analytical sample, m.p. 224–230°, $[\alpha]^{25}D$ +96.4°. The compound did not absorb in the ultraviolet; in the infrared spectrum, a hydroxyl band appeared at 2.90 μ, plus a band at 6.04 μ attributed to the Δ⁴-olefinic bond; ketal ether bands remained intact.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.57; H, 9.68.

(15) C. Djerassi and M. Gorman, *J. Am. Chem. Soc.*, **75**, 3704 (1953).

(16) Such a displacement was envisioned by Djerassi and Gorman in the formation of dithiolanes from α,β-unsaturated ketones in order to explain the fact that the double bond remains at the 4,5-position in these compounds.

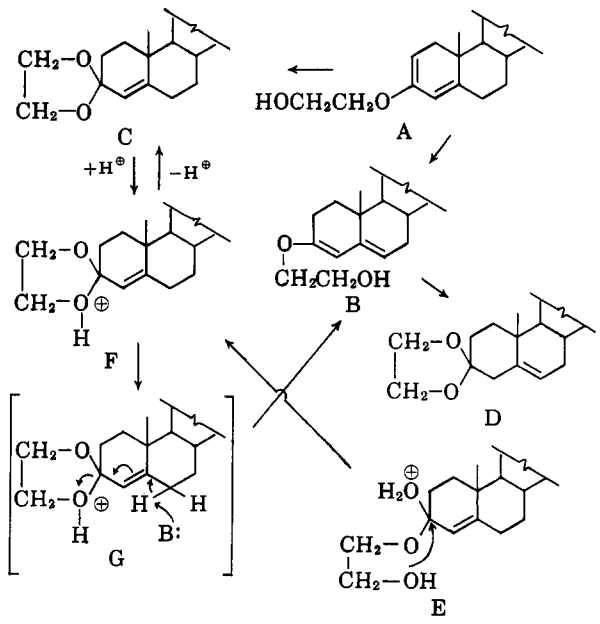

Figure 2

3,3-Ethylenedioxyandrost-4-en-17β-ol (III).—Testosterone (30.0 g., 104 mmoles) was ketalized by azeotropic distillation in 1.2 l. of benzene for 5 hr. with 0.5 g. (2.63 mmoles) of *p*-toluenesulfonic acid monohydrate and 130 ml. of ethylene glycol. The dried crude product had an ultraviolet absorption of λ_{max} 241 mμ (ε 6400), indicating that 40% of the starting ketone remained unconverted to ketal. Careful fractional crystallization of the total crude product from acetone containing a trace of pyridine gave 6.31 g. of the Δ⁴-ketal III in five crops of crystals, all melting in the range 210–230°. The yield was 30.4% based on the conversion indicated by the ultraviolet spectrum of the total product, or 18.2% over-all. Several recrystallizations from acetone provided the analytical sample, m.p. 225–232°, $[\alpha]^{25}D$ +95.1°. The infrared spectrum was identical with that of the material obtained by saponification of 17β-acetoxy compound II.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.70; H, 9.84.

From the mother liquors was obtained 5.32 g. of the Δ⁵-isomer V, m.p. 175–183° (15.4% over-all yield, or 25.6% of the total ketals). Recrystallization from methanol–*n*-hexane furnished a pure sample, m.p. 185.5–188°, $[\alpha]^{25}D$ −44.0°; lit.[2] m.p. 185–188°, $[\alpha]^{25}D$ −45.5°.

Acetylation of 3,3-Ethylenedioxyandrost-4-en-17β-ol (III).—A solution of 10.0 g. (30 mmoles) of 3,3-ethylenedioxyandrost-4-en-17β-ol in 50 ml. of pyridine and 20 ml. of acetic anhydride was heated to 100° for 1 hr., then left at room temperature overnight. Dilution of the reaction solution with 2 l. of cold water gave a white crystalline precipitate which after air drying weighed 11.30 g. (a quantitative yield) and had m.p. 153–162°. Recrystallization from *n*-hexane containing a trace of pyridine gave 9.72 g. of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate (II), m.p. 158–160.5°; plus a second crop, 1.07 g., m.p. 155–159°.

The melting point was undepressed when mixed with a sample of the Δ⁴-ketal obtained by ketalization of testosterone acetate and the infrared spectra were identical.

Attempted Epoxidation of 3,3-Ethylenedioxyandrost-4-en-17β-ol Acetate (II).—To a solution of 1.0 g. (2.7 mmoles) of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate in 70 ml. of anhydrous ether was added a molar equivalent of monoperphthalic acid[17] as a solution in anhydrous ether (1.47 ml. of a 1.82 *M* solution). The solution was held at 5° for 2 days, then at room temperature for a day; a starch–potassium iodide test for peracid was then negative. The solution was diluted with 50 ml. of ether and was washed with 25 ml. of 2 *N* sodium hydroxide followed by three 25-ml. portions of water. Concentration of the ether solution to a small volume by boiling afforded 0.85 g. of white crystalline solid, m.p. 148–155°. An infrared spectrum of this material showed that it was essentially unchanged from starting material.

(17) E. E. Royals and L. L. Harrell, *J. Am. Chem. Soc.*, **77**, 3405 (1955).

3,3-Ethylenedioxyandrosta-4,6-dien-17β-ol (VIII).—Androsta-4,6-dien-17β-ol-3-one (VII, 23.0 g., 80 mmoles, m.p. 203–205°) was ketalized by azeotropic distillation in 1.9 l. of benzene for 24 hr. with 1.16 g. (6.1 mmoles) of *p*-toluenesulfonic acid monohydrate and 116 ml. of ethylene glycol. The crude product was noncrystalline; column chromatography on Florisil afforded the ketal VIII as white needles (7.95 g., 30.0%), eluted with 20% ether in *n*-pentane. Further elution of the column with ether allowed the recovery of 8.5 g. of starting material.

One recrystallization from ether containing a drop of pyridine gave 5.96 g. of slightly impure ketal, m.p. 178–181°. Several recrystallizations from a mixture of ether and hexane plus a trace of pyridine gave the analytical sample, m.p. 181.2–183.0°, $[\alpha]^{25}D$ +88.9°. The infrared spectrum was consistent with the assigned structure, and ultraviolet absorption was observed at λ_{max} 239 mμ (ε 25,200), 234 (sh) (23,800), and 248 (sh) (15,700).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.00; H, 8.87.

3,3-Ethylenedioxyandrosta-4,6-dien-17β-ol Acetate (IX).—A solution of 7.00 g. (21.2 mmoles) of 3,3-ethylenedioxyandrosta-4,6-dien-17β-ol in 10 ml. of pyridine and 5 ml. of acetic anhydride was heated at 100° for 30 min. and then cooled in ice. The crystals that separated were collected by suction filtration and washed with cold ether and *n*-hexane. After drying, the product weighed 4.28 g. (54.3%) and had m.p. 160–162.5°. Recrystallization from *n*-hexane afforded an analytical sample, m.p. 163–164.5°, $[\alpha]^{25}D$ +61.1°. With the exception of acetate absorption bands now present in the infrared spectrum, the ultraviolet and infrared spectra were identical with those of the 17β-hydroxy ketal VIII.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.45; H, 8.33.

6α-Bromo-3,3-ethylenedioxyandrost-4-en-17β-ol Acetate (X).—A mixture of 2.0 g. (5.34 mmoles) of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate (II) and 0.96 g. (5.40 mmoles) of N-bromosuccinimide in 100 ml. of dry carbon tetrachloride was refluxed for 3 min. while being irradiated with an incandescent bulb; the solution then gave a negative starch–potassium iodide test. Filtration and evaporation of the filtrate gave an oil which crystallized readily. Recrystallization of the crude product from ether gave the bromo ketal acetate X as three crops of crystals totaling 1.45 g. (59.9% of theory). Two recrystallizations from ether provided analytically pure material, m.p. 161–162° dec., $[\alpha]^{25}D$ −72.6°. A melting point determined in an evacuated Pyrex capillary was unchanged from one determined in an open capillary.

Anal. Calcd. for $C_{23}H_{33}BrO_4$: C, 60.92; H, 7.34; Br, 17.63. Found: C, 60.92; H, 7.46; Br, 17.88.

Dehydrohalogenation of Bromo Ketal Acetate X with Lithium Bromide and Lithium Carbonate in Dimethylformamide.—The entire crude product from the N-bromosuccinimide bromination of 3.75 g. (10 mmoles) of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate was dissolved in 55 ml. of dry dimethylformamide. Lithium carbonate (2.68 g., 40 mmoles) and lithium bromide (3.47 g., 40 mmoles) were added. (Both salts had been dried *in vacuo* at 100°.) The yellow mixture was heated at 100° and stirred mechanically for 17 hr. After cooling to room temperature, the reaction mixture was diluted with 1 l. of cold water and stirred for 1 hr. The product was extracted with six 100-ml. portions of methylene dichloride which were combined and dried over sodium sulfate. Evaporation of the filtered extract gave 15 ml. of a dimethylformamide solution of the product. This solution was diluted with 400 ml. of water and the oily precipitate was extracted with ether in three 250-ml. portions. The combined ether extract was dried over sodium sulfate, filtered, and concentrated by boiling; *n*-pentane was added to the warm ether solution until crystallization began. The mixture was cooled in ice and filtered, affording 1.84 g., m.p. 122–132°. A second crop, 0.22 g., m.p. 122–145°, was obtained from the filtrate. Analysis of the ultraviolet spectrum of the total crude product (63% of theory) showed it to be a mixture of 27% of 3,3-ethylenedioxyandrost-4,6-dien-17β-ol acetate (characteristic absorption at 235, 238, and 247 mμ) and 63% of androsta-4,6-dien-17β-ol-3-one acetate (characteristic absorption at 283 mμ). Recrystallization from aqueous methanol containing a few drops of 2 *N* hydrochloric acid resulted not only in hydrolysis of the minor ketal component but also in hydrolysis of the 17β-acetoxyl function. There was obtained 1.38 g. (48.1%) of slightly impure androsta-4,6-dien-17β-ol-3-one (VII), m.p. 180–190°. A mixture melting point with authentic material (m.p. 202–204°) was undepressed; further recrystallization of the impure material gave the pure compound, identical in all respects with an authentic sample.

Attempted Dehydrohalogenation of X with *s*-Collidine.—The total crude bromo ketal derived from the N-bromosuccinimide bromination of 10 mmoles of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate was dissolved in a mixture of 50 ml. of dry xylene and 2.0 ml. (1.83 g., 15 mmoles) of *s*-collidine (b.p. 169–171°). The solution was heated under reflux for 30 min. and then cooled to room temperature. It was evident from the very small quantity of collidine hydrobromide which had precipitated that dehydrohalogenation was far from complete. Distillation at reduced pressure was employed to remove most of the xylene, after which 35 ml. of *s*-collidine was added to the residue. The solution was distilled at atmospheric pressure through a 3-in. Vigreux column until the vapor temperature had reached 156°. The fractionating column was replaced by a reflux condenser and the collidine solution was boiled for 30 min. After cooling to room temperature and dilution with 100 ml. of ether, the mixture was filtered to collect precipitated collidine hydrobromide, which after drying amounted to 0.76 g., or 37.6%. The ethereal filtrate was evaporated, affording a residual collidine solution that was diluted with 600 ml. of cold water. The sticky solid which precipitated was collected by filtration and recrystallized from a mixture of ether and *n*-pentane. There was obtained 2.37 g. of needlelike crystals in three crops, each melting in the vicinity of 160° with decomposition. An infrared spectrum of the major fraction was identical with that of authentic 6α-bromo-3,3-ethylenedioxyandrost-4-en-17β-ol acetate (X) and a bromine analysis provided confirmation.

Anal. Calcd. for $C_{23}H_{33}BrO_4$: Br, 17.7. Found: Br, 18.1.

The undehydrohalogenated bromo ketal constituted 52.3% of the starting material. The filtrate gave only dark oily material which could not be induced to crystallize.

When a solution of 500 mg. of pure X in 10 ml. of *s*-collidine was heated under reflux for 3 hr. and was then worked up as indicated earlier, there was isolated 0.54 g. of crude product, m.p. 199° dec. This compound was probably a collidine complex of bromo compound, for on recrystallization from aqueous ethanol there was recovered 400 mg. (80%) of the starting bromo ketal, identified by its melting point, optical rotation, and the identity of its infrared spectrum with that of an authentic sample of X.

Acetonolysis of 6α-Bromo-3,3-ethylenedioxyandrost-4-en-17β-ol Acetate (X).—A solution of 500 mg. (1.1 mmoles) of 6α-bromo-3,3-ethylenedioxyandrost-4-en-17β-ol acetate and 50 mg. of *p*-toluenesulfonic acid monohydrate in 20 ml. of dry acetone was left at room temperature for 16 hr. After dilution with 20 ml. of ether plus 20 ml. of *n*-hexane, the solution was washed with 20 ml. of dilute sodium bicarbonate solution, two 20-ml. portions of water, and then with 20 ml. of saturated brine. The ether–hexane solution was dried briefly over anhydrous sodium sulfate and was then filtered and concentrated by boiling until crystallization began. Three crops of platelike crystals were obtained, totaling 360 mg., or 80% of the theoretical yield of bromo ketone. Recrystallization from ether–*n*-pentane afforded 275 mg. of pure 6α-bromotestosterone acetate (XII), m.p. 145–146° dec., $[\alpha]^{25}D$ +57.6°. Ultraviolet absorption was λ_{max} 237 mμ (ε 13,600). A mixture melting point with authentic 6α-bromotestosterone acetate (see following text) was undepressed and the infrared spectra were identical.

Attempted Epimerization of 6β-Bromotestosterone Acetate[7] under Mild Conditions.—Conditions identical to those employed for the acetonolysis of the bromo ketal X were used. A solution of 1.00 g. (2.44 mmoles) of 6β-bromotestosterone acetate and 0.10 g. of *p*-toluenesulfonic acid monohydrate in 40 ml. of acetone was left at room temperature for 16 hr. The solution was diluted with 40 ml. of ether and 40 ml. of *n*-hexane and was then washed with 40 ml. of dilute sodium bicarbonate, two 40-ml. portions of water, and 40 ml. of saturated brine. After brief drying over anhydrous sodium sulfate, the ether–hexane solution was filtered and concentrated by boiling until crystallization began from the hot solution. Needle-like crystals (700 mg.) were obtained, m.p. 119.5–123° dec. A mixture melting point with starting material (m.p. 147–148° dec.) was intermediate, m.p. 136–138.5°. Without further purification, the product was examined in the ultraviolet: λ_{max} 244 mμ (ε 13,000). Its optical rotation was $[\alpha]^{25}D$ −1.9°. The extent of change from the properties of pure 6β-bromotestosterone acetate ($[\alpha]^{25}D$ −13° and λ_{max} 248 mμ (ε 13,300)) indicated that epimerization of bromo ketone occurred to only a minor extent under the same conditions as were employed for acetonolysis of the bromo ketal X.

6α-Bromotestosterone Acetate (XIII).—Bromination of testosterone acetate in carbon tetrachloride solution with a molar equivalent of N-bromosuccinimide under strong irradiation with an incandescent bulb gave 6β-bromotestosterone acetate, m.p. 147–148° dec., $[\alpha]^{25}D$ −13.0°, λ_{max} 248 mμ (ε 13,300). The yield of purified product was 56.8% and the physical properties agreed with those reported[7] for the compound. A portion was then epimerized to the 6α-bromo (equatorial) epimer by the procedure of Bowers and co-workers.[14]

Dry hydrogen chloride was bubbled through a solution of 1.00 g. (2.44 mmoles) of 6β-bromotestosterone acetate in 100 ml. of glacial acetic acid for 25 min. at room temperature. After standing for 30 min. longer, the solution was diluted with 2 l. of cold water to afford a solid precipitate. The crude product was collected on a filter and washed with water, then air dried. The slightly sticky solid was dissolved in ether and the solution was dried over anhydrous potassium carbonate. After filtration, the ether solution was diluted with *n*-pentane and concentrated by boiling until the product crystallized as plates, m.p. 133–135° dec. One recrystallization from ether–*n*-hexane afforded pure 6α-bromotestosterone acetate XII, m.p. 147–148° dec., $[\alpha]^{25}D$ +54.8°. Ultraviolet absorption was at λ_{max} 237 mμ (ε 13,600).

Anal. Calcd. for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.33; H, 7.18; Br, 19.48.

Ketalization of Testosterone Acetate with Differing Low Concentrations of Acid Catalyst.—Testosterone acetate (5.0 g., 15.1 mmoles) was ketalized azeotropically in benzene solution (350 ml.) with 20 ml. of ethylene glycol and 25 mg. of *p*-toluenesulfonic acid. The reaction was carried out by heating at reflux under a water trap for 7 hr. The mixture was then cooled to room temperature and washed with dilute sodium bicarbonate and several times with water. Evaporation of the benzene solution to dryness under reduced pressure gave a solid crystalline residue which was examined for ultraviolet absorption.

The experiment was repeated with 50 mg. of acid catalyst, then with 75 mg. The three experiments represented catalyst concentrations of 0.00037 *M*, 0.00074 *M*, and 0.00111 *M*, respectively. The crude product of each reaction absorbed at 241 mμ in the ultraviolet, indicative of unchanged testosterone acetate. Calculations showed the extent of reaction in each case to be (a) 0.00037 *M* catalyst, 49% conversion to ketal; (b) 0.00074 *M* catalyst, 65% conversion to ketal; and (c) 0.00111 *M* catalyst, 75% conversion to ketal.

Isomerization of Testosterone Acetate Δ^4-Ketal II to Its Δ^5-Isomer VI.—A solution of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate (II, 1.00 g., 2.6 mmoles) and 50 mg. (0.26 mmole) of *p*-toluenesulfonic acid monohydrate in 100 ml. of dry benzene was heated under reflux for 3 hr., with the condensate returning through a Dean–Stark water separator. After cooling to room temperature, the solution was washed with dilute sodium bicarbonate, then three times with water. After brief drying over sodium sulfate, the benzene solution was distilled to dryness under reduced pressure to afford a solid residue which was recrystallized from a mixture of acetone and *n*-hexane, 0.45 g., m.p. 180–189° (a 45% yield). No further crystalline material could be obtained from the filtrate. One additional recrystallization from acetone containing a trace of pyridine gave pure 3,3-ethylenedioxyandrost-5-en-17β-ol acetate, m.p. 201–204°, $[\alpha]^{25}D$ −50.9°; lit.[2] m.p. 203–205°, $[\alpha]^{29}D$ −52.1°. A mixture melting point with authentic material was undepressed and a comparison of infrared spectra showed no differences.

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The Base-Catalyzed Self-Condensation of 2-Ethyl-2-hexenal. III. Structure of Isomeric Glycols, $C_{16}H_{30}O_2$[1]

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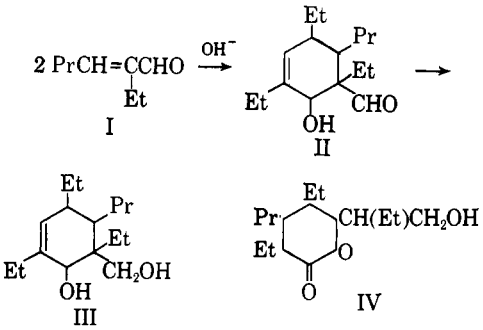
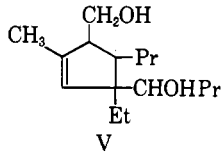
The self-condensation of 2-ethyl-2-hexenal by heating under reflux with aqueous sodium hydroxide produces four glycol diastereoisomers, $C_{16}H_{30}O_2$ (III) (25% total yield), and previously described[4] lactones, $C_{16}H_{30}O_3$ (IV) and $C_{12}H_{22}O_2$ (XIV). The glycols have all been shown to be 6-hydroxymethyl-5-propyl-2,4,6-triethyl-2-cyclohexen-1-ols by degradation (two routes) to known 3-propyl-2,4,6-triethylphenol (VIII). They are each produced from the corresponding aldol (II) in a crossed Cannizzaro reaction by oxidation of butanal and 2-ethyl-2-hexenal.

In the previous papers of this series[3,4] the self-condensation of 2-ethyl-1-hexenal (I) was reported to produce three C_{16} products: an aldol, $C_{16}H_{28}O_2$ (II), a glycol, $C_{16}H_{30}O_2$ (III, 32% yield), and a lactone, $C_{16}H_{30}O_3$ (IV) in the presence of aqueous methanolic potassium hydroxide at 25°. Lithium aluminum hydride reduction of II gave III, obtained as a liquid. Publishing simultaneously and independently, Pummerer and Smidt[5] also described the self-condensation of I, employing aqueous sodium hydroxide at reflux temperature (110°). They reported the formation of two diastereoisomeric glycols, $C_{16}H_{30}O_2$ (22% total yield), one of m.p. 62° and one a liquid, and to both they assigned a five-membered ring structure (V). Since it seemed unlikely to us that the difference in reaction conditions in the two experiments[4,5] was suf-





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