lized from acetone–petroleum ether, 280 mg., m.p. 210–215° dec. Recrystallization from acetone–petroleum ether gave the pure 16α-propionate, m.p. 219–222° dec., $[\alpha]^{22}\text{D}$ +56.4°, $\lambda_{\max}$ 239 mμ (ε 15,600); $\lambda_{\max}^{\text{KBr}}$ 2.93, 3.41, 5.75, 5.80, 6.00, 6.16, 6.21, 8.44, 8.86, 9.21, 9.37, 9.50, 11.20 μ, etc.; papergram mobility, system V, R_f 0.05; system VI, R_f 0.04.

Anal. Calcd. for $C_{24}H_{31}O_7F$: C, 63.99; H, 6.94; F, 4.22. Found: C, 64.27; H, 7.33; F, 4.22.

Acylation of Va with propionic anhydride–pyridine yielded triamcinolone 16α,21-dipropionate (Vc), m.p. 178–181°, identical with the authentic sample.

9α - Fluoro - 11β,17α - dihydroxy - 16α,21 - dipropionoxy-1,4-pregnadiene-3,20-dione (Vc).—Five hundred milligrams of triamcinolone was acylated with 5 ml. of propionic anhydride and 10 ml. of pyridine. After standing overnight the product was isolated in the usual manner and recrystallized twice from acetone–petroleum ether, 220 mg., m.p. 181–183°, $[\alpha]^{22}\text{D}$ +67.0°, $\lambda_{\max}$ 238 mμ (ε 15,300); $\lambda_{\max}^{\text{KBr}}$ 2.90, 3.40, 5.72, 5.77, 5.99, 6.15, 6.20, 8.43, 11.18 μ, etc.; papergram mobility, system V, R_f 0.67; system VI, R_f 0.45.

Anal. Calcd. for $C_{27}H_{35}O_8F$: C, 64.02; H, 6.96; F, 3.75. Found: C, 63.81; H, 7.16; F, 4.15.

21 - Acetoxy - 9α - fluoro - 11β - hydroxy - 16α,17α - methoxymethylenedioxy - 1,4 - pregnadiene - 3,20 - dione (III).—A solution of 300 mg. of triamcinolone methyl orthoformate derivative IIb in 4 ml. of dry pyridine was treated with 0.8 ml. of acetic anhydride. After 16 hours the reaction was terminated by addition of methanol and removal of solvents *in vacuo*. The residue was crystallized from acetone–petroleum ether to yield impure crystals which, on recrystallization from the same solvent pair, weighed 240 mg., m.p. 188–191°. After two recrystallizations more the orthoester acetate was obtained, m.p. 192–194°, $[\alpha]^{22}\text{D}$ +123°, $\lambda_{\max}$ 238 μ (ε 15,620); $\lambda_{\max}^{\text{KBr}}$ 2.92, 3.39, 5.70(shoulder), 5.75, 5.98, 6.15, 6.20, 8.17, 8.85, 9.32, 9.42, 9.70, 10.05, 11.16, etc.; $\lambda_{\max}^{H_2SO_4}$ ($E_{1\,\text{cm}}^{1\,\%}$): 2 hr., 260 (257), 309 (116), 380 mμ (17); 20 hr., 260 (274), 309 (116), 374 mμ (104); papergram mobility, system V, R_f 0.93; system VI, R_f 0.72; positive to tetrazolium blue and to isonicotinic acid hydrazide.

Anal. Calcd. for $C_{25}H_{31}O_8F$: C, 62.75; H, 6.53; F, 3.97. Found: C, 62.98; H, 6.91; F, 4.01.

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Some Reactions of 2-Hydroxytestosterone and its Diacetate. I

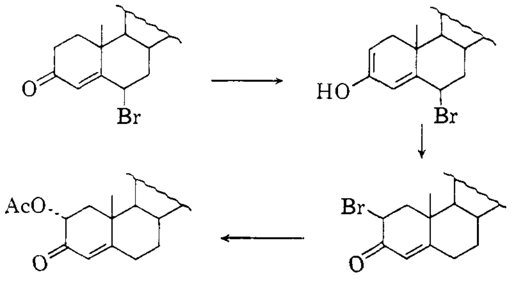
BY ROBERT L. CLARKE

RECEIVED MARCH 1, 1960

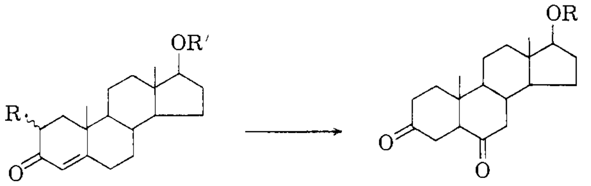
Treatment of 2β-hydroxytestosterone diacetate (Ia) with *p*-toluenesulfonic acid in methanol produced 17β-hydroxy-5α-androstan-3,6-dione. Oxidation of Ia, its 2α-epimer Ib or 2α-hydroxytestosterone with molecular oxygen under alkaline conditions gave 2,17β-dihydroxy-1,4-androstadien-3-one (IIIa).

Rivett and Wallis[1] reported that 6β-bromo-4-cholesten-3-one reacted with potassium acetate in acetic acid to give "6α-acetoxy-4-cholesten-3-one." Fieser and Romero[2] later showed that this reaction product actually was 2α-acetoxy-4-cholesten-3-one and suggested a possible mechanism for the rearrangement as shown by equation A. This same reaction has been observed with 6β-bromotestosterone acetate.[3,4] The present paper reports a reaction which is essentially the reverse of this rearrangement, *i.e.*, a 2→6-migration.

A



In the course of continuing investigations of 2-oxygenated steroids in this Laboratory, 2β-hydroxytestosterone diacetate[3] (Ia) was subjected to the action of *p*-toluenesulfonic acid (tosyl acid) in boiling methanol. 17β-Hydroxy-5α-androstane-3,6-dione[3] (IIa) (51% yield) and its acetate[5] (IIb) (4% crude yield) were isolated from the reaction mixture as the only products identified. For characterization purposes the 3,6-dione IIa was converted to its acetate ester[5] and to 5α-androstane-3,6,17-trione.[6]



Ia, R = β-OAc, R' = Ac
b, R = α-OAc, R' = Ac
c, R = α-OH, R' = H

IIa, R = H
b, R = Ac

This 2→6-rearrangement is dependent upon substantially anhydrous conditions. The presence of 5% water prevents it. Lowering the reaction temperature to 26° also essentially stops the process. The rate of reaction is dependent upon the concentration of the tosyl acid. For example, using 200 mg. of Ia and 10 mg. of tosyl acid, the ultraviolet absorption of the solution due to the unsaturated ketone chromophore dropped by 56% in 48 hr. With a fivefold increase in tosyl acid concentration the absorption dropped by 92% in 8 hr. When 200 mg. of 2α-hydroxytestosterone diacetate (Ib) was refluxed with methanol containing 10 mg. of tosyl acid, a drop of only 10% in ultraviolet absorption occurred in 48 hr. The rearrangement propensity thus appears related to the β-configuration at C-2.

The mechanism of the rearrangement is perhaps that shown by equation B. The water required for

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(1) D. E. A. Rivett and E. S. Wallis, *J. Org. Chem.*, **15**, 35 (1950).

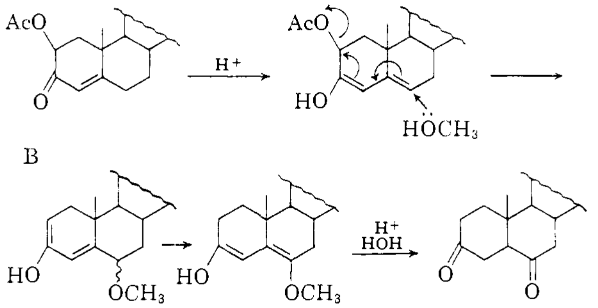
(2) L. F. Fieser and M. A. Romero, THIS JOURNAL, **75**, 4716 (1953).

(3) F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *ibid.*, **75**, 4712 (1953).

(4) R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini, *ibid.*, **77**, 661 (1955).

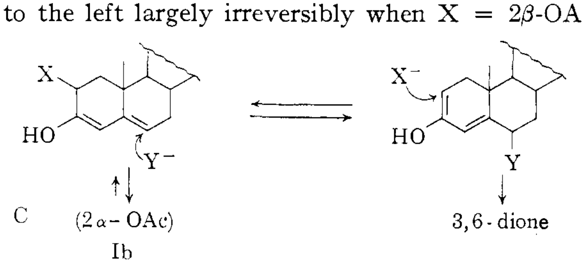
(5) S. H. Eppstein, P. D. Meister, H. M. Leigh, D. H. Peterson, H. C. Murray, L. M. Reineke and A. Weintraub, *ibid.*, **76**, 3174 (1954).

(6) C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1587 (1952).

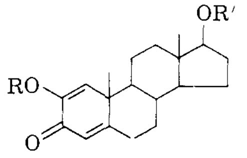


hydrolysis of the intermediate enol methyl ether could have come from the solvent or by esterification of the acetic acid formed in the reaction. All attempts to isolate the intermediate enol ether failed.[7]

It is plausible that an equilibrium such as is shown in equation C may exist which is driven to the right irreversibly under the presently reported conditions (where X = β-OAc and Y = ξOCH_3) and to the left largely irreversibly when X = 2β-OAc and Y = Br. It should be noted that 2β-hydroxytestosterone diacetate (unstable 2-configuration) was isolated from the reaction of 6β-bromotestosterone acetate with potassium acetate in acetic acid[4] as well as the 2α-epimer[3] and that under the reaction conditions epimerization of the 2β- to the 2α-configuration occurs.[4] The mechanism of reaction proposed by Fieser and Romero would not account for the formation of the 2β-acetoxylated product. If 2-bromotestosterone were indeed formed it would have to appear in both configurations to explain the mixture of acetoxylated products.[7a]



Rivett and Wallis[1] described the hydrolysis of what actually was 2α-hydroxy-4-cholesten-3-one acetate (see above) to form 2α-hydroxy-4-cholesten-3-one which "gives a purple coloration with ferric chloride." Fieser and Romero[2] repeated this hydrolysis and confirmed the ferric chloride coloration, noting also the formation of a yellow enolate salt. In our laboratory, hydrolysis of 2β- or 2α-hydroxytestosterone diacetate[3] with potassium bicarbonate and especially with potassium hydroxide resulted in the formation of 2α-hydroxytestosterone[3] together with a by-product which gave a purple coloration with ferric chloride. This by-product, separable by chromatography in ether–pentane on silica gel, was 2,17β-dihydroxy-1,4-androstadien-3-one (IIIa), recently reported by Baran.[8] Its properties, together with those of its 2,17-diacetate IIIb, corresponded with those reported by Baran who prepared it by bismuth trioxide oxidation of 2α-hydroxytestosterone and by selenium dioxide oxidation of testosterone. Its infrared spectrum was identical with that of a sample of IIIa prepared by Baran's selenium dioxide procedure,[8] and admixture of the two samples did not depress their melting points.



IIIa, R = R′ = H
b, R = R′ = Ac

Production of the dienone IIIa during the hydrolysis described was due to air oxidation under alkaline conditions.[8a] Simply bubbling oxygen through a suspension of 2β- or 2α-hydroxytestosterone diacetate in aqueous methanol containing potassium hydroxide produced the dienone IIIa in 70 and 54% yields, respectively. Observation of the ultraviolet light absorption of the reaction mixture revealed that the initial band present at 243 mμ largely disappeared within 1 hr. and was replaced by a band at 248 mμ. The 248 mμ band then disappeared with simultaneous appearance of a 254 mμ band which was produced by the dienone IIIa. The optimum time for the reaction was about 7 hr.

It was believed initially that the appearance of the 248 mμ band was due to rapid oxidation with formation of 2,17β-dihydroxy-1,4-androstadien-3-one diacetate (IIIb) (λ_{max}^{EtOH} 248 mμ) followed by slow hydrolysis to form IIIa (λ_{max}^{EtOH} 254 mμ). However, O_2 oxidation of 2α-hydroxytestosterone (Ic) produced the same intermediate 248 mμ absorption and a 58% yield of IIIa. The ultraviolet absorption data indicated little difference in the rates of formation of IIIa from the 2β-acetoxy-, the 2α-acetoxy- or the 2α-hydroxy compounds (Ia, Ib and Ic, respectively).

Pure 2α-hydroxytestosterone gave no coloration with ferric chloride. Probably the ferric chloride coloration obtained with 2α-hydroxy-4-cholesten-3-one[1,2] was due to the presence of some 2-hydroxy-1,4-cholestadien-3-one.

Experimental[9]

Rearrangement of 2β-Hydroxytestosterone Diacetate (Ia).—A solution of 2.0 g. of 2β-hydroxytestosterone diacetate[3] and 0.25 g. of anhydrous p-toluenesulfonic acid in

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[7] These attempts involved neutralizing the tosyl acid in the reaction mixture with sodium methoxide before work-up.

[7a] NOTE ADDED IN PROOF.—Additional evidence that the 2β-acetoxy compound is initially formed in this rearrangement is furnished by the recent observation of P. N. Rao and L. R. Axelrod, THIS JOURNAL, **82**, 2830 (1960), that this 2β-epimer can be isolated in 45% yield if the reaction is run for 10 min. whereas the yield drops to 21%[4] at the end of 4 hr.

[8] J. S. Baran, *ibid.*, **80**, 1687 (1958).

[8a] NOTE ADDED IN PROOF.—Rao and Axelrod (note 7a) reported that repetition of previously described experiments[3] involving hydrolysis of 2α- and 2β-hydroxytestosterone diacetates (Ia and Ib) to form 2α-hydroxytestosterone (Ic) gave them no Ic but only the 1,4-dienone IIIa. We have found that the ratio of Ic to IIIa produced depends on the degree of exclusion of oxygen both from the *solvents* and the adjacent atmosphere. Boiling the solvents in a nitrogen stream prior to addition of the steroid and maintenance of a nitrogen atmosphere prevents formation of IIIa.

[9] All melting points are corrected. The silica gel used for chromatography was 100–200 mesh obtained from the Davison Chem. Co., Baltimore, Md. Appreciation is expressed to the Analytical and Physical Chemistry Departments of this Institute for their analytical and spectral data.

350 ml. of methanol was refluxed for 8 hr. The solvent was removed *in vacuo* and the residue was dissolved in ether. This solution was washed with 2*N* sodium hydroxide solution and water and dried over magnesium sulfate. The ether solution was concentrated to a volume of 150 ml., diluted with 350 ml. of pentane and poured onto a column of 75 g. of silica gel. Gradual enrichment of the eluting solvents to a 3:2 ether–pentane mixture gave 0.07 g. (4% yield) of crude **17β-hydroxy-5α-androstane-3,6-dione acetate** (IIb) which was identified by infrared spectral comparison with a sample described below. Elution with 7:3 ether–pentane afforded 1.07 g. of **17β-hydroxy-5α-androstane-3,6-dione (IIa)** which was recrystallized once from acetone to give 0.80 g. (51% yield) of white crystals, m.p. 232–236°, $[\alpha]^{25}\text{D}$ −10.0° (1% in $CHCl_3$), $\lambda_{\max}^{\text{EtOH}}$ 286 mμ (ε 48), $\lambda_{\max}^{\text{KBr}}$ 2.88 μ (OH) and possible doublet at 5.84–5.87 μ [reported 235–236°, $[\alpha]^{20}\text{D}$ +9° ($CHCl_3$)[10]]. The mother liquors furnished a further 0.053 g. of IIa, m.p. 226–234°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.25. Found: C, 74.7; H, 9.3.

The acetate of IIa, prepared with acetic anhydride in pyridine, melted at 183–186°, $[\alpha]^{25}\text{D}$ −15.3° (1% in $CHCl_3$) [reported[5] m.p. 185–186°, $[\alpha]^{25}\text{D}$ −17° (0.9% in $CHCl_3$)].

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.79; H, 8.73. Found: C, 72.7; H, 9.1.

Androstane-3,6,17-trione.—17β-Hydroxy-5α-androstane-3,6-dione (400 mg.) was oxidized by chromic anhydride in acetic acid[11] and the product recrystallized from acetone–pentane to give 175 mg. of needles, m.p. 192–194°, $[\alpha]^{25}\text{D}$ +72.6° (0.85% in $CHCl_3$) $\lambda_{\max}^{CS_2}$ 5.71 and 5.79 μ [reported[6] m.p. 191.5–192.5°, $[\alpha]^{28}\text{D}$ +71° (1% in $CHCl_3$)].

Reaction rate measurements on the 2→6-rearrangement were made by periodically allowing the reaction to cool just sufficiently to stop its boiling, withdrawing 1.00-ml. aliquots of the mixture and diluting the aliquots to a 100-ml. volume with 95% grain alcohol. The presence of the water in the alcohol served to prevent further reaction in the aliquot. The optical density of the diluted aliquots was then measured in the 230–280 mμ range with a Cary ultraviolet spectrophotometer. The data shown below were obtained when 200 mg. of Ia was dissolved in 40 ml. of methanol at its boiling point, a zero time aliquot was withdrawn, and 50 mg. of anhydrous tosyl acid was added. The values recorded are qualitative only since temperature effects in the sampling process were disregarded and no correction was made for the zero time optical density which would be increased by the presence of the tosyl acid to be added.

Time, hr.	$\lambda_{\max}^{\text{EtOH}}$, mμ	Opt. den.	Decrease, %
0	243	2.02	0
1	240	1.29	36
2	240	0.73	64
4	240	.30	85
8	243	.16	92

Oxidation of 2β-Hydroxytestosterone Diacetate (Ia).—A partial solution of 6.0 g. (0.0155 mole) of pulverized 2β-hydroxytestosterone diacetate, m.p. 199–201°, in 250 ml. of 95% ethanol was treated with a solution of 4.0 g. of potassium hydroxide (assay 85%) in 150 ml. of water at room temperature and the mixture was stirred vigorously while a stream of oxygen was bubbled through it. All of the solid dissolved within 30 min. Stirring was stopped, but the gas addition was continued for a total of 7 hr. Acetic acid (5 ml.) was added and the colorless solution was concentrated to a 225-ml. volume by warming *in vacuo*. The precipitated **2,17β-dihydroxy-1,4-androstadien-3-one** (IIIa) was collected from the cooled mixture, air-dried and recrystallized from ethyl acetate to give 3.3 g. (70% yield) of rods and prisms, m.p. 207–209°, $[\alpha]^{25}\text{D}$ −16.2 (1% in $CHCl_3$), $\lambda_{\max}^{\text{EtOH}}$ 254 mμ (ε 14,600), 290 mμ (s) (ε 3100) [reported[8] m.p. 207–209°, $[\alpha]\text{D}$ −20.1° ($CHCl_3$), $\lambda_{\max}^{\text{EtOH}}$ 254 mμ (ε 15,400)]. This product showed no depression in melting point upon admixture with a sample prepared by selenium dioxide oxidation of testosterone[8] and the infrared spectra of the samples were identical.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46, H, 8.67. Found: C, 75.7; H, 8.9.

The diacetate of IIIa (IIIb), prepared with acetic anhydride in pyridine and purified by chromatography on silica gel followed by recrystallization from methanol, was formed in 75% yield, m.p. 208.5–209.5°, $[\alpha]^{25}\text{D}$ +12.6° (1% in $CHCl_3$), $\lambda_{\max}^{\text{EtOH}}$ 248 mμ (ε 16,600) [reported[8] m.p. 205–206°, $[\alpha]\text{D}$ + 20.2° ($CHCl_3$), $\lambda_{\max}^{\text{EtOH}}$ 247.5 mμ (ε 16,750)].

Oxidation of 2α-Hydroxytestosterone Diacetate (Ib).—Oxidation of Ib was performed in a manner identical with that for Ia to give a 54% yield of once recrystallized IIIa, m.p. 203–205°. A second recrystallization from ethyl acetate raised the melting point only to 203.5–205.5°, $\lambda_{\max}^{\text{EtOH}}$ 254 mμ (ε 14,200) 290 mμ (s) (ε 3100). The infrared spectra of this material and that prepared from Ia were superimposable. There was no depression in melting point upon admixture of the two samples.

Oxidation of 2α-Hydroxytestosterone (Ic).—Oxidation of Ic was performed in a manner identical with that for Ia except that the product melted low and was, therefore, chromatographed on silica gel (1.6 g. on 100 g. of adsorbant) in ether–pentane. The concentration of ether was gradually increased from 30 to 60%. The eluted product was recrystallized from ethyl acetate to give a 58% yield of III, m.p. 206–209°, $\lambda_{\max}^{\text{EtOH}}$ 254 mμ (ε 14,200), 290 (s) mμ (ε 3100). The infrared spectra of this material and of the dienone prepared from Ia were superimposable. There was no depression in melting point upon admixture of the two samples.

Reaction rate measurements on the oxidations described above were made by periodically withdrawing 1.00-ml. aliquots of the reaction mixture and adding them to 99 ml. of 95% grain alcohol containing 1 ml. of 0.1 *N* aqueous acetic acid. The acid conditions stopped the reaction in the aliquot. The optical density of the diluted aliquots was then measured in the 230–280 mμ range with a Cary ultraviolet spectrophotometer. The data shown below were obtained when oxygen was bubbled through a solution of 100 mg. of Ia in 14 ml. of absolute alcohol to which was added 6 ml. of water contining 75 mg. of potassium hydroxide (assay 85%). The values are only qualitative since a slight error due to evaporation of the solvent was not taken into account.

Time, hr.	$\lambda_{\max}^{\text{EtOH}}$, mμ	Opt. den.	$\lambda_{\max}^{\text{EtOH}}$, mμ	Opt. den.	$\lambda_{\max}^{\text{EtOH}}$, mμ	Opt. den.
0	243	1.95				
1	243(s)[a]	1.50	248	1.60	253	1.54
2			248	1.59	253	1.63
4			248(s)[a]	1.55	253	1.66
7					253	1.66

[a] Shoulder.

RENSSELAER, N. Y.

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[10] Note discrepancy in sign of rotation.

[11] *Cf.* oxidation of 3β,17β-dihydroxy-5α-androstan-6-one, H. B. MacPhillamy and C. R. Scholz, THIS JOURNAL, **74**, 5512 (1952).