a homogeneous solution. The ammonia was distilled, affording 1.85 g of crystalline material. Recrystallization from acetone gave 1.15 g of the pure triol: mp 217–219°; λ_{max} 2.72 μ; Δν [$(CD_3)_2SO$] 37(18-CH_3), 51 (19-CH_3), and 61 (21-CH_3) cps; $[\alpha]_D$ 52 (MeOH).

Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.52; H, 10.97.

Hydride reduction of 1.0 g of methyl desoxybisnorcholanate by procedure B gave 0.67 g of the same triol.

Acknowledgment.—We wish to thank Dr. Hugh L. Dryden, Jr., for several stimulating discussions pertaining to the theoretical aspects of this paper.

The Enol Acetylation of 3-Oxo 5β-Steroids

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Received November 1, 1965

The enol acetylation of 17β-acetoxy-5β-androstan-3-one has been investigated under conditions of kinetic and thermodynamic control. Both methods lead to mixtures of enol acetates. The results of thermodynamically controlled enol acetylation are discussed in terms of nonbonded interactions in the enolic forms of the parent ketone.

During an investigation of structure–reactivity relationships it became necessary to find a model keto steroid which has a dual enolization. The 3-oxo steroids of the 5α series such as cholestan-3-one (**3c**) are known to form a single Δ^2-enol since bromination[1,2] and sulfonation[3,4] yield C-2 monosubstituted products. An examination of the literature revealed that the 3-oxo 5β-steroids present a more ambiguous pattern of enolization since bromination of 5β-cholestan-3-one (**2c**) gave only a 40% yield of the 4β-bromo-5β-cholestan-3-one (**5b**).[1] Bromination–dehydrobromination studies with this compound have yielded reaction products whose ultraviolet spectra suggested the presence of some 5β-cholest-1-en-3-one (**8b**).[5] Similarly, sulfonation of 5β-cholestan-3-one gave a mixture of C-2 and C-4 monosubstituted products.[3,4] In contrast with these results, enamine formation with 5β-cholestan-3-one (**2c**) led to a single Δ^3-enamine[6] and enol acetylation using acetyl chloride–acetic anhydride[7] or isopropenyl acetate[8] yielded only 3-acetoxy-5β-cholest-3-ene (**6b**). Steric considerations discussed below suggested that some of the less favored Δ^2-enol of 3-oxo 5β-steroids should be formed. For these reasons it was decided to investigate the enolization of 3-oxo 5β-steroids.

Enol acetylation was chosen for this study since the compounds are easily prepared and can be readily analyzed by gas chromatography.[9] There are several methods for preparing enol acetates and Hartshorn and Jones[10] and Berkoz, Chavez, and Djerassi[11] have shown that the ratio of enol acetates formed depends on the reaction conditions chosen and that bromination, which proceeds *via* the intermediate enols, does not necessarily parallel the enol acetylation results. It is essential for this study that the enol acetylation conditions chosen reflect the enolization properties of the parent ketone. In studying the enolization of 3,3-dimethylcyclohexanone, it was demonstrated[12] that the perchloric acid catalyzed acetic anhydride enol acetylation[13] was thermodynamically controlled and each isomeric enol acetate, when subjected to the acetylating conditions, was capable of regenerating the equilibrium mixture. It was also demonstrated that the ratio of enol acetates formed under equilibrium conditions corresponded to the bromination and nitric acid oxidation results.

The steroid model used for this investigation was 17β-acetoxy-5β-androstan-3-one (**2a**). The compound was prepared by catalytic hydrogenation of testosterone (**1b**) using palladium catalyst[14,15] to yield a 3:1 ratio of 5β and 5α isomers **2b** and **3b**, respectively. The 5β isomer can be isolated by fractional crystallization of the corresponding acetates **2a** and **3a**. Column chromatography with Florisil was required to obtain pure 5α isomer **3a**.

The perchloric acid catalyzed enol acetylation of carbonyl compounds is often accompanied by dark intractable material,[9] and it was found expedient to use the isopropenyl acetate–sulfuric acid method[8] to prepare the enol acetates of **2a** in sufficient quantity for purification and identification. Gas–liquid partition chromatographic (glpc) analysis of the reaction product revealed 71% 3,17β-diacetoxy-5β-androst-3-ene (**6a**) and 29% 3,17β-diacetoxy-5β-androst-2-ene (**7a**).

Proof of the isomeric nature of the two enol acetates was obtained by saponifying the reaction product under mild conditions.[16] Glpc and thin layer chromatography (tlc) detected a single saponification product, identified as 17β-acetoxy-5β-androstan-3-one (**2a**).

The enol acetates **6a** and **7a** were separated by preparative glpc and their nmr spectra were recorded. The major constituent of the mixture of enol acetates showed a vinylic proton singlet at 5.05 ppm. The compound was tentatively assigned the Δ^3-enol acetate

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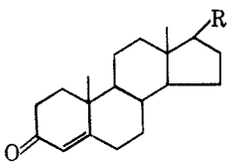

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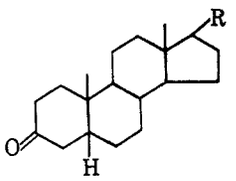

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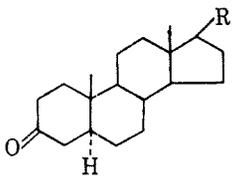

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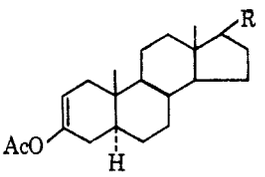

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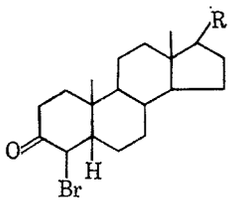

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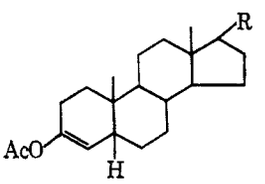

6a, R = OAc
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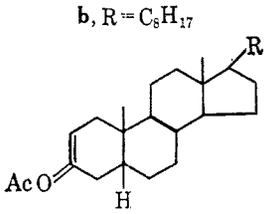

7a, R = OAc
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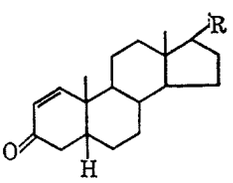

8a, R = OAc
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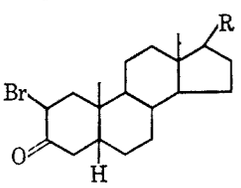

9a, R = OAc
b, R = C_8H_{17}

structure **6a** since the coupling between the vinylic hydrogen and the hydrogen at C-5 should be minimal because the bonds of these hydrogens form a dihedral angle of approximately 90°. The minor constituent was tentatively assigned the Δ^2-enol acetate structure **7a** because of the multiplet centered at 5.27 ppm. The nmr spectra of the individual enol acetates did not provide conclusive evidence for structural assignments. Since 3-oxo 5α-steroids such as 17β-acetoxy-5α-androstan-3-one (**3a**) form only Δ^2-enol acetates,[8] a comparison of the proton spectra of 3,17β-diacetoxy-5α-androst-2-ene (**4a**) with 3,17β-diacetoxy-5β-androst-2-ene (**7a**) should corroborate the previous structural assignments.

Enol acetylation of 17β-acetoxy-5α-androstan-3-one (**3a**) with isopropenyl acetate afforded 3,17β-diacetoxy-5α-androst-2-ene (**4a**) in good yield. Glpc analysis confirmed the presence of a single Δ^2-enol acetate **4a**. The nmr spectrum of the compound showed a multiplet centered at 5.29 ppm which was similar to that of the minor constituent in the mixture of enol acetates **6a** and **7a**.

A chemical proof of structure for the enol acetates **6a** and **7a** was needed to rigorously establish their identity. The major constituent was isolated by preparative glpc and brominated in the presence of epichlorohydrin to minimize rearrangement and to afford kinetically controlled products.[17] The bromo ketone whose infrared spectrum had a single carbonyl band at ν_{max} 1730 cm^{-1} was identical with 17β-acetoxy-4β-bromo-5β-androstan-3-one (**5a**) reported by Fieser and Huang.[18] Dehydrobromination using lithium carbonate in dimethylformamide[10] followed by glpc analysis indicated that the crude product was composed of 65% testosterone acetate (**1a**), 20% 17β-acetoxy-5β-androstan-3-one (**2a**), and 14% 17β-acetoxy-5β-androst-1-en-3-one (**8a**).

The minor component in the enol acetate mixture, 3,17β-diacetoxy-5β-androst-2-ene (**7a**), was separated by preparative glpc and brominated using the procedure described above. Despite mild brominating conditions[17] the infrared spectrum, ν_{max} 1730 cm^{-1}, indicated that the initial product of bromination was 17β-acetoxy-2β-bromo-5β-androstan-3-one (**9a**).[19] The bromo ketone was stable to hydrobromic acid[20] and could be isolated unaltered after 24 hr at room temperature. The equatorial bromine in **9a** probably arose from bromination of the half-boat conformation,[21] although rapid isomerization of the sterically crowded axial bromo ketone may be responsible for the observed bromination results.[22] The bromo ketone **9a** was dehydrobrominated as previously described and glpc of the crude product demonstrated 78% 17β-acetoxy-5β-androst-1-en-3-one (**8a**), 9.5% testosterone acetate (**1a**), and 12.6% 17β-acetoxy-5β-androstan-3-one (**2a**). The major constituent (**8a**) of this dehydrobromination mixture was prepared in larger quantity for characterization by enol acetylation of **2a** followed by bromination–dehydrobromination of the isomeric mixture of enol acetates **6a** and **7a**. The conjugated ketones **1a** and **8a** were then isolated by preparative tlc. The 17β-acetoxy-5β-androst-1-en-3-one structure was confirmed by infrared (ν_{max} 1678 cm^{-1}) and ultraviolet (λ_{max} 232 mμ)[23] spectroscopy.

By analogy with the work carried out with 5β-cholestan-3-one (**2c**) in which there was reported[8] the exclusive formation of the Δ^3-enol acetate **6b**, it had been anticipated that 17β-acetoxy-5β-androstan-3-one (**2a**) would form a single enol acetate **6a**. The formation of 29% of the isomeric enol acetate **7a** appeared anomalous; however, Favre and Baczynskyj[24] have also detected comparable quantities of the Δ^2-enol acetate **7b** on repeating the isopropenyl acetate enol acetylation of 5β-cholestan-3-one (**2c**). Recently,

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TABLE I

NONBONDED INTERACTIONS IN THE ENOLIC FORMS OF 3-OXO 5β-STEROIDS

Δ³-Enol	r, cm	Kcal/mole	Δ²-Enol	r, cm	Kcal/mole
αH(C-2)–αH(C-9)	4.3	1.29	αH(C-4)–αH(C-7)	4.4	0.96
CH_3(C-19)–βH(C-8)	6.7	0.85	αH(C-4)–αH(C-9)	5.3	0.12
CH_3(C-19)–βH(C-6)	7.0	0.45	CH_3(C-19)–βH(C-8)	6.5	1.25
CH_3(C-19)–βH(C-1)	7.2	0.26	CH_3(C-19)–βH(C-6)	6.3	1.78
CH_3(C-19)–αH(C-1)	7.0	0.45	CH_3(C-19)–βH(C-1)	6.7	0.85
CH_3(C-19)–βH(C-5)	6.9	0.56	CH_3(C-19)–αH(C-1)	7.2	0.27
CH_3(C-19)–βH(C-11)	6.4	1.48	CH_3(C-19)–βH(C-5)	7.0	0.45
αH(C-1)–αH(C-11)	5.0	0.23	CH_3(C-19)–βH(C-11)	6.7	0.82
			αH(C-1)–αH(C-11)	4.4	0.98
Total		5.57	Total		7.48

Smith and Chen[25] have shown that a sealed tube isopropenyl acetate enol acetylation is initially kinetically controlled with thermodynamic control becoming a significant factor in the latter stages of the reaction. It is possible that the discrepancy between the published isopropenyl acetate enol acetylation results with 3-oxo 5β-steroids[3] and those obtained here may be due in part to the rate at which the acetone formed during the reaction is removed by distillation. If the acetone is not removed efficiently, equilibration could diminish the amount of Δ²-enol acetate in the reaction product.

The enol acetates of 17β-acetoxy-5β-androstan-3-one **6a** and **7a** were then formed under thermodynamically controlled conditions[12] using perchloric acid catalyst and acetic anhydride. The equilibrium mixture was obtained after 20 hr at room temperature. Glpc on the crude product indicated that the mixture consisted of 43% starting material **2a** and 57% enol acetates which were present in a ratio of 93.5 parts of 3,17β-diacetoxy-5β-androst-3-ene (**6a**) and 6.5 parts of 3,17β-diacetoxy-5β-androst-2-ene (**7a**). A mixture of 65% **6a** and 35% **7a** was subjected to these reaction conditions and the equilibrium mixture of 94:6 of **6a** to **7a** was obtained after 3.5 hr.

Djerassi has suggested that two main factors operate in determining the direction of enol acetylation and probably enolization in 3-oxo 5α-steroids.[11] The first is steric and involves angular methyl group interactions, while the second is hyperconjugative. The following calculations of nonbonded interactions are intended to demonstrate that the direction of enolization of the 3-oxo 5β-steroids is also governed by steric forces in the absence of any hyperconjugative effect.

Previous work has shown that Hill's method of calculating H–H and CH_3–H interactions[26] may be used to estimate the relative stabilities of the two enolic forms of a ketone.[27] The agreement between calculated and experimental results using the perchloric acid catalyzed enol acetylation was sufficiently interesting to warrant extending the work to the steroid series.

In calculating the relative stabilities of the two enolic forms, **6a** and **7a**, of 17β-acetoxy-5β-androstan-3-one (**2a**) a number of assumptions were made: (i) the A ring of the 3-oxo 5β-steroid assumes the classical half-chair conformation in the enolic form: (ii) the B ring of the steroid assumes a geometrically perfect chair form; (iii) nonbonded interactions are additive; and (iv) the acetate group has no influence on the relative stability of the two enol acetates. None of the first three assumptions would be expected to hold in all cases since large nonbonded interactions could cause skeletal deformations; however, the interactions involved in these cases are relatively small and the distortions are considered minimal. Using Hill's formula

$$U = -2.25\epsilon(r^*/r)^6 + (8.28 \times 10^5)\epsilon \exp(-r/0.0736r^*)$$

and the values of r^* and ϵ^* given therein,[26] the nonbonded interactions listed in Table I were calculated from r values (average of ten readings) measured on Dreiding models.

The calculated difference between the two enols is 1.91 kcal/mole, which corresponds to an equilibrium mixture of 96% Δ³-enol and 4% Δ²-enol. Experimentally 93.5% Δ³- and 6.5% Δ²-enol were found. These results suggest that steric forces are the dominant factor which governs enol acetylation and enolization. Thus, the enolic double bond formed in preponderance will be the one in which there is the most facile accommodation of substituents on the A, B, and C rings of the steroidal ketone. However, it should be noted that essentially the same order of stabilities for the two enols is obtained if one neglects the C-11 interactions, Δ³ 3.86 kcal/mole, Δ² 5.68 kcal/mole, or a difference of 1.82 kcal/mole which can explain the results quite satisfactorily. Further experiments are underway to assess the contribution from the C-11 position.

Experimental Section

General.—Melting points were determined on an Electrothermal apparatus by the capillary method and are corrected. Rotations were measured in chloroform solution at 25°. The infrared spectra were recorded in carbon tetrachloride solution using a Perkin-Elmer Model 221 double-beam spectrophotometer. The ultraviolet spectra were determined in 95% ethanol solution using a Bausch and Lomb Spectronic 502 recording spectrophotometer. The nmr spectra were determined on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The adsorbant for thin layer chromatography was Merck Silica Gel G and the solvent was benzene–ethanol (8:1). Gas chromatography was carried out on a Model 810 F & M gas chromatograph equipped with dual flame detectors. The columns were 5% Fluoro Silicone FS-1265 (QF-1) on 60–80 mesh Diatoport "S", 8 ft long × 4 mm o.d. The carrier gas was helium at a flow rate of 60 ml/min and the column temperature was 225°. Quantitative estimation of mixtures was made by triangulation of the signals.

Preparative glpc was carried out with an 8 ft long × ½ in. o.d. column using the same liquid phase and column support material. The helium flow rate was regulated to 450 ml/min.

17β-Acetoxy-5β-androstan-3-one (2a).—A mixture of testosterone (**1b**, mp 154°, 5 g) in 95% ethanol (100 ml) containing 3 *N* hydrochloric acid (8 ml) and 10% palladium-on-charcoal catalyst (250 mg) was hydrogenated at ambient pressure and

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temperature by shaking in an atmosphere of hydrogen.[17] After the stoichiometric uptake of hydrogen (0.75 hr) the catalyst was removed by filtration and washed with acetone. The combined washings and ethanolic solution were diluted with water (100 ml) and concentrated to half-volume (100 ml) under reduced pressure. The suspension was extracted with 50 ml of ether (twice), the organic layer was washed with bicarbonate and salt solutions, dried over sodium sulfate, and filtered, and the solvent was evaporated. The crystalline residue (mp 125–129°, 4.97 g) was gas chromatographed and a single poorly defined peak was obtained. Acetylation by the usual method using pyridine–acetic anhydride afforded a mixture (4.8 g) which, when analyzed by gas chromatography, was shown to consist of 74% 5β isomer **2a** and 26% 5α isomer **3a** (retention times 15.2 and 16.4 min, respectively). Recrystallizations from acetone–hexane gave pure 5β isomer **2a** (1.7 g) which was homogeneous by glpc and tlc: mp 140–142°, (lit.[28] mp 140–142°), $[\alpha]^{25}D$ +45.2° (*c* 0.53), infrared ν_{max} 1709 cm^{-1} (C=O) and 1731 cm^{-1} (—$OCOCH_3$).

17β-Acetoxy-5α-androstan-3-one (3a).—The residual material (2.9 g), after isolating the 17β-acetoxy-5β-androstan-3-one (**2a**), was chromatographed over 225 g of Florisil and the column was eluted with 8:2 hexane–ether. The 17β-acetoxy-5α-androstan-3-one (**3a**) was eluted from the column after the 5β isomer **2a**. Crystallization from acetone–hexane afforded 800 mg of **3a**, homogeneous by glpc and tlc: mp 160°, $[\alpha]^{25}D$ +30° (*c* 0.98), (lit.[28] mp 158–159°, $[\alpha]^{20}D$ +31.5°), infrared ν_{max} 1725 (—$OCOCH_3$) and 1710 cm^{-1} (>C=O).

Isopropenyl Acetate Enol Acetylation of 17β-Acetoxy-5β-androstan-3-one (2a).—A solution of **2a** (2.5 g) in isopropenyl acetate (25 ml) containing concentrated sulfuric acid (0.02 ml) was refluxed under nitrogen for 1 hr, the pressure was reduced, and the solvent was partially distilled (10 ml) in the course of 0.5 hr. The remaining solution was chilled, diluted with ether (100 ml), and washed with sodium bicarbonate and salt solutions. After drying over sodium sulfate, the solvent was distilled leaving a brown crystalline material (2.3 g). Glpc on the crude product demonstrated peaks with retention times 6.0 and 7.2 min, which represented 71% 3,17β-diacetoxy-5β-androst-3-ene (**6a**) and 29% 3,17β-diacetoxy-5β-androst-2-ene (**7a**).

A sample (200 mg) of the enol acetate mixture **6a** and **7a** was dissolved in ethanol (5 ml) and saturated sodium carbonate solution (3 ml) was added. The suspension was stirred at room temperature for 4 hr and the solvents were evaporated. The residue was extracted with methylene chloride (20 ml) and the extract was washed with salt solution till neutral. The solution was dried over sodium sulfate and the solvent was evaporated. The crude product was acetylated by the usual method using pyridine–acetic anhydride. The crude 17β-acetoxy-5β-androstan-3-one (**2a**) crystallized after removal of the solvent and trituration with ether, mp 139–142°, mixture melting point undepressed. Glpc of the crude material revealed one peak at retention time 16.0 min (peak enhanced by authentic material).

Preparative glpc on an aliquot of the mixture (1.1 g) gave pure 3,17β-diacetoxy-5β-androst-3-ene (**6a**, 110 mg) which failed to crystallize from the usual solvents. Sublimation at 105° and 3×10^{-3} mm yielded crystalline **6a** (90 mg): mp 102–103°; $[\alpha]^{25}D$ +61° (*c* 0.95) (lit.[28] mp 102–103°; $[\alpha]^{20}D$ +35.5°); infrared ν_{max} 1752 (>C=C—$OCOCH_3$), 1735 (—$OCOCH_3$), and 1689 cm^{-1} (>C=C<). The nmr spectrum showed a vinyl proton, singlet at 5.05 ppm (peak width at half-height 4 cps).

The second enol acetate 3,17β-diacetoxy-5β-androst-2-ene (**7a**) was isolated by preparative glpc and crystallized from acetone–hexane (60 mg): mp 119–121°; $[\alpha]^{25}D$ +98.0° (*c* 0.55); infrared spectrum ν_{max} 1754 (>C=C—$OCOCH_3$), 1735 (—$OCOCH_3$), and 1700 cm^{-1} (>C=C<). The nmr spectrum showed a vinyl proton unresolved multiplet centered at 5.27 ppm (peak width at half-height 13 cps).

Anal.[29] Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.68; H, 9.10.

Isopropenyl Acetate Enol Acetylation of 17β-Acetoxy-5α-androstan-3-one (3a).—A solution of **3a** (95 mg) was treated as described above and glpc of the crude product (101 mg) showed a single peak at retention time 23 min. Column chromatography over 10 g of Florisil and elution with 1:1 benzene–ether afforded a colorless product which was crystallized from ethanol (55 mg): mp 169–170°; $[\alpha]^{26}D$ +38.8° (*c* 1.04) (lit.[28] mp 173–174°; $[\alpha]^{20}D$ +41°); infrared ν_{max} 1750 (>C=C—$OCOCH_3$), 1735 (—$OCOCH_3$), and 1693 cm^{-1} (>C=C<). The nmr spectrum showed a vinyl proton unresolved multiplet centered at 5.29 ppm (peak width at half-height 12 cps).

Acetic Anhydride–Perchloric Acid Enol Acetylation of 17β-Acetoxy-5β-androstan-3-one (2a).—A mixture of acetic anhydride (1.2 ml) and 70% perchloric acid (0.02 ml) was added to a stirred solution of 17β-acetoxy-5β-androstan-3-one (**2a**) (50 mg) in benzene (8 ml) and carbon tetrachloride (3 ml). After a reaction period of 20 hr at room temperature the solution was diluted with carbon tetrachloride (10 ml) and washed with 5% sodium bicarbonate and salt solutions, dried over sodium sulfate, filtered, and the solvent evaporated leaving a dark semisolid (44 mg): infrared ν_{max} 1753 (>C=C—$OCOCH_3$), 1731 (—$OCOCH_3$), and 1708 cm^{-1} (>C=O). Glpc of the crude product demonstrated peaks at 6.0 [3,17β-diacetoxy-5β-androst-3-ene (**6a**)], 7.2 [3,17β-diacetoxy-5β-androst-2-ene (**7a**)], and 23 min [17β-acetoxy-5β-androst-3-one (**2a**)]. Each peak was identified by peak enhancement with pure material. The ratio of enol acetates **6a** and **7a** was 93.5 to 6.5, respectively, while 43% of the product was unreacted starting material **2a**. The yield of enol acetates corrected for starting material was 83%. Prolonging the reaction time did not alter the ratio of the peaks but increased the yield of intractable material.

Equilibration of Enol Acetates 6a and 7a.—A crystalline mixture (50 mg) of the enol acetates consisting of 65% **6a** and 35% **7a** was treated as above. Glpc analysis of the reaction mixture after 3.5 hr indicated that the crude product consisted of 3.3% **2a** and 96.7% enol acetates **6a** and **7a** in a ratio of 94:6, respectively. The compounds were identified by peak enhancement with authentic material.

17β-Acetoxy-4β-bromo-5β-androstan-3-one (5a).—The enol acetate **6a** (90 mg) was dissolved in a mixture of carbon tetrachloride (2.0 ml) and epichlorohydrin (0.1 ml). A chilled solution of bromine (41 mg) in carbon tetrachloride (0.25 ml) was added to the steroid. The reaction mixture was stirred at 0° until the color of bromine disappeared (8 min). The solvent was evaporated leaving an oil which was kept *in vacuo* at 60° for 30 min. The 17β-acetoxy-4β-bromo-5β-androstan-3-one (**5a**) (98 mg) was crystallized from acetone–hexane: mp 174–176°, $[\alpha]^{26}D$ +54.7° (lit.[18] mp 174–175°, $[\alpha]D$ + 44.7°), infrared ν_{max} 1730 cm^{-1} (—$OCOCH_3$ and >C=O). An aliquot (25 mg) of crystalline **5a** was dissolved in acetic acid (10 ml) containing a trace of concentrated hydrobromic acid (0.02 ml) and kept at room temperature for 24 hr. The solution was diluted with chloroform (40 ml), washed with sodium bicarbonate solution, dried over sodium sulfate, filtered, and the solvent evaporated. The residual oil (20.6 mg) crystallized and was identical with the starting bromo ketone **5a**, mp 174–176°, mixture melting point undepressed.

17β-Acetoxy-2β-bromo-5β-androstan-3-one (9a).—The enol acetate **7a** (22 mg) in carbon tetrachloride (0.4 ml) was treated as described above with bromine (9.5 mg) and epichlorohydrin (0.02 ml). After evaporation of the solvents, the 17β-acetoxy-2β-bromo-5β-androstan-3-one (**9a**) was crystallized from ethanol (16 mg): mp 201–202°, infrared ν_{max} 1735 cm^{-1} (—$OCOCH_3$ and >C=O).

Anal. Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.59; Br, 19.44. Found: C, 61.18; H, 7.32; Br, 19.22.

An aliquot of **9a** (5 mg) was treated with hydrobromic acid and acetic acid for 24 hr as previously described. The compound was isolated unaltered: mp 200–201°, mixture melting point undepressed.

17β-Acetoxy-androst-4-en-3-one (1a).—Testosterone (**1b**, 1.0 g) was acetylated by the usual method using pyridine–acetic anhydride. The acetate **1a** was crystallized from acetone–hexane: mp 139–141° (lit.[28] 139–141°), infrared ν_{max} 1667 cm^{-1}, and ultraviolet λ_{max} 241 mμ (log ε 4.16). Glpc analysis showed one peak at retention time 21 min.

17β-Acetoxy-5β-androst-1-en-3-one (8a).—A sample (1.0 g) of the mixture of enol acetates **6a** and **7a** from the isopropenyl acetate enol acetylation of **2a** was brominated as described above and the crude bromo ketone mixture of **5a** and **9a** (800 mg) was dissolved in dimethylformamide (25 ml) containing lithium carbonate (800 mg). The reaction mixture was heated at 110° for 2.5 hr while stirring in an atmosphere of nitrogen. The solvent was evaporated under vacuum and the residue was taken up in methylene chloride (50 ml) and washed successively with 5% hydrochloric acid, sodium bicarbonate, and salt solutions.

(28) J. Fajkos, *Chem. Listy*, **51**, 1885 (1957).

(29) Analyses were performed by Schwarzkopf Microanalytical Laboratories, New York, N. Y.

The organic solution was dried over sodium sulfate and filtered, and the solvent was evaporated leaving an oil (672 mg). The crude mixture of **1a** and **8a** was separated by preparative tlc. The plates (8 in.^{2}) were coated with a 500-μ layer of silica gel and activated overnight at 125°. The mixture (50 mg/plate) was deposited from methylene chloride solution as a 5-mm-wide band. The bands were detected by ultraviolet (R_f 0.65 and 0.73) and aspirated from the plates. The products were eluted from the adsorbant by washing with methylene chloride and filtering. The compound at R_f 0.73, 17β-acetoxy-5β-androst-1-en-3-one (**8a**), was crystallized from acetone–hexane (108 mg): mp 140–141°, $[\alpha]^{25}D$ +134° (*c* 0.53) (lit.[30] $[\alpha]D$ +141°), infrared ν_{max} 1667 cm^{-1} (>C=C—C=O), ultraviolet λ_{max} 232 mμ (log ϵ 4.22). The purity of the compound was verified by glpc (single peak at retention time 16 min).

The second tlc band (R_f 0.65) was isolated as described above and the compound crystallized from acetone–hexane: mp 139–141°. Glpc analysis and a mixture melting point with authentic 17β-acetoxy-androst-4-en-3-one (**1a**) prepared by the acetylation of **1b** were used to identify the compound.

(30) M. Pesez, J. Barlos, J. Mathieu, and J. Valls, *Bull. Soc. Chim. France*, 488 (1958).

The 17β-acetoxy-2β-bromo-5β-androstan-3-one (**9a**) (12 mg) obtained from the bromination of **7a** was subjected to the dehydrobrominating conditions described above and the crude product was analyzed by glpc. Three compounds were detected at retention times 13 (12.6% 17β-acetoxy-5β-androstan-3-one), 16 (78% 17β-acetoxy-5β-androst-1-en-3-one), and 21 min (9.5% 17β-acetoxy-androst-4-en-3-one). The identity of all peaks was verified by peak enhancement with authentic material and by infrared spectroscopy.

The dehydrobromination of 17β-acetoxy-4β-bromo-5β-androstan-3-one (**5a**, 80 mg) was carried out as described above and the crude product (64 mg) was analyzed by glpc. Three compounds were detected at retention times 13 (20% 17β-acetoxy-5β-androstan-3-one), 16 (14% 17β-acetoxy-5β-androst-1-en-3-one), and 21 min (65% 17β-acetoxy-androst-4-en-3-one). The identity of the peaks was verified by peak enhancement with authentic material and by infrared spectroscopy.

Acknowledgment.—The author wishes to thank Dr. O. E. Edwards and Dr. D. Vocelle of the National Research Council for the nmr spectra and Mr. A. J. Bayne for technical assistance.

Application of the Beckmann Rearrangement to the Preparation of A-Azapregnane Derivatives[1]

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January 14, 1966

5α-Pregnane-3,20-dione 3-oxime and A-nor-5α-pregnane-2,20-dione 2-oxime were prepared in good yield by selective oximation of the corresponding diketones. The oximation studies showed that a six-membered A-ring 3-ketone is more reactive than a five-membered A-ring 2-ketone and that both of these are more reactive than the side-chain carbonyl group at C-20. Beckmann rearrangement of these oximes gave A-homo-4-aza-5α-pregnane-3,20-dione in 93% yield, and a mixture of 3-aza-5α-pregnane-3,20-dione and 2-aza-5α-pregnane-3,20-dione in 93% yield, thus providing an excellent route to A-azapregnane derivatives.

In recent years a number of examples of the partial synthesis of A-aza steroids by the Beckmann rearrangement of oximes have been reported.[3]

However, this route has not been utilized for the preparation of A-azapregnane and A-aza-A-homopregnane derivatives from simple pregnanediones. Several examples are now reported here.

Since 5α-pregnane-3,20-dione is readily available, and A-nor-5α-pregnane-2,20-dione is relatively readily available,[4] these compounds were chosen for study. If a method of selective oximation at the 2 or 3 position in the presence of the free 20-carbonyl group could be worked out, protection of the 20-carbonyl group could be avoided, thus simplifying the partial synthesis. Accordingly, a study of the relative reactivity of these three carbonyl groups toward hydroxylamine was undertaken (Scheme I).

When 5α-pregnane-3,20-dione (I) was treated with 1 equiv of hydroxylamine at ambient temperatures 5α-pregnane-3,20-dione 3-oxime (II) was formed in 75% yield. That oximation had taken place at the 3 position was shown in the following manner. 5α-Pregnan-3β-ol-20-one (III) was converted to the known 20-oxime IV,[5] and this was oxidized with Jones reagent[6] to 5α-pregnane-3,20-dione 20-oxime (V) (30%). This oxime was obviously different from the one obtained from the 3,20-dione, thus establishing the structure of the two oximes. As a further check, 5α-pregnane-3,20-dione dioxime (VI) was prepared and subjected to levulinic acid hydrolysis[7] under mild conditions, which gave the 20-oxime V (46%) along with unreacted dioxime. These experiments show that the 3-carbonyl group in the A ring is more reactive toward hydroxylamine (and presumably related compounds such as phenylhydrazine) than the 20-carbonyl group in the side chain. They also show that the 20-oximino group is more resistant to acidic hydrolysis than the 3-oximino group.

In order to obtain the oxime of A-nor-5α-pregnane-2,20-dione (VII) it was necessary to use higher temperatures (60°) and much longer reaction times (14 days). Under these conditions with 1 equiv of hydroxylamine, A-nor-5α-pregnane-2,20-dione 2-oxime (VIII) was obtained in 74% yield (90% based on recovered starting material). The structural assignment was made on the basis of the results of the Beckmann rearrangement of the oxime described below and by the infrared spectrum. The A-nor 2-oxime had a carbonyl stretching

(1) A portion of this work was supported by the U. S. Public Health Service under Grant AM 05249-02.

(2) Abstracted from the Ph.D. Thesis of A. C. W., Jr., Brown University, 1965. Jesse Metcalf Fellow, 1962–1964.

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