249. *Steroids. Part CLXXII.* Factors Controlling the Direction of Enol Acetylation of 3-Oxo-steroids.*

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Some of the factors controlling the direction of enol acetylation (and probably also of enolization) of 3-oxo-steroids with the A/B-*trans*-junction are discussed. It is shown that, contrary to the widely held assumption that such enolization always proceeds towards $C_{(2)}$, it is possible to vary the double-bond isomer ratio so that in certain circumstances (*e.g.*, perchloric acid-catalyzed enol acetylation of a 4α-methyl-3-oxo-19-nor-steroid) enolization is exclusively in the opposite direction. Variations between the extremes are noted, and both steric and hyperconjugative factors are shown to play important roles. Nuclear magnetic resonance spectroscopy can be used to advantage in establishing the isomer ratio, as can optical rotatory dispersion of the derived products of kinetically controlled bromination.

It is generally accepted [1] that the direction of enolization of 3-oxo-steroids of the 5α-series (I) is exclusively towards position 2, as determined by the products of bromination, alkylation, and condensation. Enol acetylation with isopropenyl acetate or acetic anhydride proceeds in the same manner to give the Δ^2-enol acetate.[2] Subsequent enol acetylation and bromination studies with 2α-methyl-3-oxo-5α-steroids [3,4] (II) and their 19-nor-analogues [5] (III) also were in agreement with this conclusion and it was surprising, therefore, to find that it did not apply to unsubstituted 19-nor-3-oxo-steroids (IV). With the latter, enol acetylation leads [5] to an inseparable, sharply melting mixture of the Δ^2- and Δ^3-enol acetates, the actual composition (2 : 1) being determined by kinetically controlled bromination and analysis of the bromination products. At that point we were informed

* Part 171, *Acta Endocrinol.*, in the press.

[1] See Fieser and Fieser, " Steroids," Reinhold Publ. Corp., New York, 1959, especially pp. 276—284.

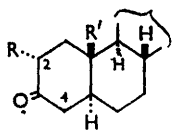
[2] Dauben, Micheli, and Eastham, *J. Amer. Chem. Soc.*, 1952, **74**, 3852; Rubin and Armbrecht, *ibid.*, 1953, **75**, 3513.

[3] Mazur and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.

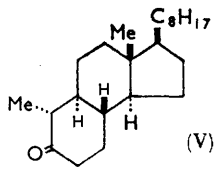
[4] Djerassi, Finch, Cookson, and Bird, *J. Amer. Chem. Soc.*, 1960, **82**, 5488; Mauli, Ringold, and Djerassi, *ibid.*, p. 5494.

[5] Villotti, Ringold, and Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 5693.

by Professor E. R. H. Jones of experiments under way in his laboratory [6] demonstrating that the direction of enol acetylation of the tricyclic ketone (V) was influenced markedly by the reaction conditions. Consequently it was agreed to carry out similar studies on related 4α-methyl-3-oxo-5α-steroids and to publish the results simultaneously.



(I : R=H;R'= Me)
(II : R=R' = Me)
(III: R=Me, R'= H)
(IV : R=R'= H)



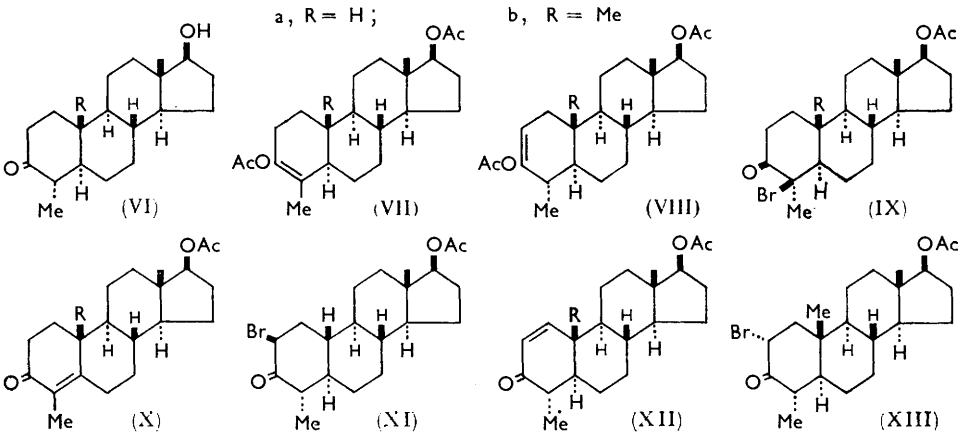
(V)

The bicyclic environment around the carbonyl group of a 4α-methyl-3-oxo-19-nor-5α-steroid is identical with that existing in the tricyclic ketone (V). Consequently, we selected the 4α-methyl-19-nor derivative (VIa) of dihydrotestosterone as the substrate since it was related stereochemically to compound (V) and would lend itself to direct comparison with the 19-nor derivative (IV) [5] and its 2α-methyl derivative (III) studied earlier.[5]

4-Methyl-19-nortestosterone [7] (Xa, as free alcohol) was reduced with lithium in liquid ammonia, affording the required 5α-dihydro-ketone (VIa), which was transformed into its enol acetate with acetic anhydride–carbon tetrachloride in the presence of perchloric acid.[8] In the 19-nor-series (IV), lacking the 4α-methyl group, it was necessary to establish the composition of the enol acetate mixture by bromination [5] since no physical method was available which could distinguish between the two possible double-bond isomers. The situation is considerably simplified with the 4α-methyl homologue (VIa) since recourse can be taken to nuclear magnetic resonance spectroscopy,[9] the Δ^3-acetate (VIIa) possessing no olefinic proton, while one such proton is present in the Δ^2-isomer (VIIIa). Such examination showed the crude enol acetate to contain no more than 5% of the Δ^2-isomer (VIIIa) and this was confirmed by kinetically controlled bromination in the presence of sodium acetate.[4] Examination of the total, crude bromination product by optical rotatory dispersion [10] demonstrated a negative Cotton effect, whose trough [11] ($[\alpha]_{330}$ −2285°) was nearly identical with that of the purified bromo-ketone (IXa) ($[\alpha]_{332\cdot5}$ −2555°). The bathochromic displacement of this trough, when compared with the position (305 mμ) of the first extremum of the Cotton effect of the halogen-free ketone (VIa) requires [12] an axial orientation for the bromine atom, while according to the axial α-halogeno-ketone rule,[13] a negative Cotton effect is only consistent with a 4β-bromo-3-oxo-formulation (IXa). As was to be expected, dehydrobromination of the bromo-ketone (IXa) with lithium bromide and lithium carbonate in dimethylformamide [14] provided 4α-methyl-19-nortestosterone (Xa), uncontaminated by its Δ^1-isomer (XIIa). The perchloric acid-catalyzed enol acetylation of the 4α-methyl-19-nor-derivative of dihydrotestosterone (VIa) thus represents the first instance where enolization in a 3-oxo-5α-steroid has been reversed completely from position 2 to position 4. These results are also in accordance with the observation [6] that enol acetylation of the tricyclic ketone (V) under similar conditions leads unilaterally to the 5,10- rather than 5,6-unsaturated isomer.

[6] Hartshorn and Jones, *J.*, preceding paper.
[7] Atwater, *J. Amer. Chem. Soc.*, 1960, **82**, 2847.
[8] Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747.
[9] See Roberts, "Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959; Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, London, 1959.
[10] Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill, New York, 1960.
[11] For nomenclature see Djerassi and Klyne, *Proc. Chem. Soc.*, 1957, 55, and chapter 2 in ref. 10.
[12] Djerassi, Osiecki, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 1216.
[13] Djerassi and Klyne, *J. Amer. Chem. Soc.*, 1957, **79**, 1506.
[14] Joly and Warnant, *Bull. Soc. chim. France*, 1958, 367.

Enol acetylation of compound (VIa) with isopropenyl acetate gave a mixture of the two enol acetates (VIIa) and (VIIIa) in an approximately 1 : 1 ratio as determined by nuclear magnetic resonance analysis. Kinetically controlled bromination of this enol acetate mixture now furnished a crude bromo-ketone, which could not be separated into its constituents by chromatography. Dehydrobromination of this bromo-ketone mixture,



followed by chromatography, afforded 55% of Δ^1- (XIIa) and 45% of Δ^4-ketone (Xa) in, good agreement with the conclusions from the earlier analysis. The ultraviolet [15] and infrared [16] spectral properties of the bromo-ketone mixture indicated the virtually exclusive presence of axial bromine and this was confirmed by the position [12] of the first rotatory dispersion extremum ($[\alpha]_{330}$ +420°). The mixture of bromo-ketones is therefore represented correctly by a 1 : 1 mixture of the axial 2β- and 4β-bromo-4α-methyl-3-ketones (XIa and IXa); and while the former could not be obtained pure the peak of its positive Cotton effect can now be calculated as $[\alpha]_{330} \sim +3300°$ from the trough of the pure 4β-bromo-ketone (IXa) and the peak of the 1 : 1 mixture of (IXa) and (XIa). These results are again in reasonable agreement with those of Hartshorn and Jones [6] for enol acetylation of the tricyclic ketone (V) promoted by isopropenyl acetate, indicating that the factors responsible for the direction of enolization under different enol acetylating conditions reside largely in the bicyclic ketonic environment (see below).

To complete the series of 3-oxo-5α-steroids for proper evaluation of the responsible factors, we needed a 4α-methyl-3-oxo-steroid containing the 19-methyl group. The only relevant experiment recorded is that of Mazur and Sondheimer [3] who noted that with isopropenyl acetate 4α-methylcholestan-3-one gave an enol acetate, which after bromination and dehydrobromination led to 4α-methylcholest-1-en-3-one. They concluded, therefore, that the enol acetate was the Δ^2-isomer, but it is not possible to determine from their work whether the Δ^3-isomer was not also formed. For our purposes, we selected 17β-hydroxy-4α-methyl-5α-androstan-3-one [17] (VIb), which was again prepared by lithium–ammonia reduction of 4-methyltestosterone (Xb, as free alcohol).[7,18] Enol acetylation by the perchloric acid procedure [8] furnished a crude mixture, which contained between 10 and 20% of unchanged ketone as judged from the relative heights of the 17-acetate and enol acetate nuclear magnetic resonance peaks (see below). This complicated somewhat the

[15] See Cookson, *J.*, 1954, 282.
[16] See Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[17] First prepared in our laboratory by E. Necoechea and H. J. Ringold, by catalytic hydrogenation of (Xb) and separation of the resulting mixture of 5α- and 5β-isomers.
[18] Ringold and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 602; Camerino, Cattapan, Valcavi, and Patelli, *Gazzetta*, 1959, **89**, 674.

quantitative estimation of the enol acetate isomers, but by using the relative areas of the olefin peak (315 c./sec.) and the peak (276 c./sec.) due to the 17α-hydrogen atom in a pure sample of the enol acetate it could be determined that there were present 65—70% of the Δ^3-enol acetate (VIIb) and 30—35% of the Δ^2-isomer (VIIIb). Kinetically-controlled bromination followed by chromatography on silica gel separated the pure acetate (IXb), whose ultraviolet spectral and optical rotatory dispersion properties (negative Cotton effect with trough at 332·5 mμ) agreed with the structural assignment, which was confirmed by dehydrobromination to 4-methyltestosterone acetate (Xb). While the pure 2α-bromo-isomer (XIII) could not be isolated in this chromatogram, it was available from another experiment described below and the rotatory dispersion curves of the pure bromo-ketones from both enol acetates (VIIb and VIIIb) were thus available. With this information it was possible to determine the composition (80% of IXb; 20% of XIII) of the total *crude* bromination mixture of the crude enol acetate from its rotatory dispersion curve (negative Cotton effect with trough at $[\alpha]_{322\cdot5}$ −1085°) which again is in reasonable agreement with the examination of the enol acetate mixture by nuclear magnetic resonance spectroscopy.

The enol acetylation of compound (VIb) by the isopropenyl acetate procedure was more complicated, because nuclear magnetic resonance as well as the bromination–dehydrobromination indicated the presence of appreciable amounts of unchanged ketone.*

Nuclear magnetic resonance afforded at least semiquantitative conclusions to be drawn for these ketone–enol acetate mixtures. All spectra were measured in deuteriochloroform solution with a Varian 60 mc. high-resolution spectrometer, with tetramethylsilane as internal standard. All signals are reported as c./sec. as well as in terms of the τ [19] and δ [20] scales.

The important peaks in the nuclear magnetic resonance spectrum of the ketone (VIb) and its enol acetates (VIIb and VIIIb) are those due to the 18-methyl group (48 c./sec.; τ 9·2, δ 0·8), the methyl-hydrogen atoms of the 17-acetoxy-group (123 c./sec.; τ 7·95, δ 2·05), and the single 17-hydrogen atom (triplet centred at 276 c./sec.; τ 5·40, δ 4·60). Features characteristic of the parent ketone (VIb) are the fine structure just down-field from the acetate peak with the most pronounced peak at 138 c./sec. (τ 7·70, δ 2·30) (probably associated with hydrogen adjacent to the 3-oxo-function) and the 19-methyl peak at 65 c./sec. (τ 8·92, δ 1·08). The latter occurs at 52 c./sec. in the enol acetates (VIIb and VIIIb). The 4-methyl group can be seen for the ketone (VIb) and the enol acetate (VIIIb) as a doublet at 55 and 62 c./sec. (τ 9·08 and 8·97, δ 0·92 and 1·03), while in the enol acetate (VIIb) this is shifted down-field in a very characteristic manner to a singlet at τ 8·53, δ 1·47 (88 c./sec.). Both enol acetates (VIIb and VIIIb) exhibit a sharp peak at τ 7·86 (δ 2·14) (128 c./sec.) due to the three enol acetate protons, while the latter also shows a peak at τ 4·73 (δ 5·27) (316 c./sec.) corresponding to the olefinic 2-proton.

Visually, mutual contamination among the three compounds is easily discernible, but quantitative evaluation is somewhat more complicated. Neverthless, it can be stated with fair confidence that the crude product obtained on treatment of the ketone (VIb) with isopropenyl acetate contains about 50% of unchanged ketone, while the remainder (judging from the relative areas of the τ 4·93 and 5·40 peaks) consists of a 7·5 : 2·5 mixture of (VIIIb) and (VIIb). This conclusion was substantiated by an examination of the nuclear magnetic resonance spectrum of a purified sample of the enol acetylation mixture from which most of the unchanged ketone had been removed [as can be seen from the close correspondence in intensity of the two acetate peaks at τ 7·95 and 7·86 (δ 2·05 and 2·14)] and which now contains 70—80% of the enol acetate (VIIIb). Essentially the

* Probably because the ketone takes up bromine only very slowly under conditions (presence of sodium acetate) where the enol acetates (VIIb) and (VIIIb) react quickly.

[19] Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.
[20] Djerassi, Nakano, James, Zalkow, Eisenbraun, and Shoolery, *J. Org. Chem.*, 1961, **26**, 1192.

same quantitative results were obtained when this purified enol acetate was brominated and the rotatory dispersion curve of the total bromination product was measured.

Kinetically controlled bromination of the enol acetate mixture followed by chromatography afforded the pure 2α-bromo-4α-methyl-acetate (XIII), the equatorial nature of the bromine atom following from the ultraviolet absorption spectrum and especially the rotatory dispersion curve (positive Cotton effect with peak at $[\alpha]_{307\cdot5}$ +736°). Dehydrobromination of the crude bromination product (before chromatography) led to the Δ^1-ketone (XIIb) and substantial amounts of the saturated starting ketone (VIb), whose presence had already been indicated by the nuclear magnetic resonance spectrum. The last eluates in the chromatogram of the dehydrobromination product contained some 4-methyltestosterone acetate (Xb), as shown by its ultraviolet absorption maximum.

In summary, it appears that two factors operate in determining the direction of enol acetylation (and probably also of enolization itself) in 3-oxo-steroids of the 5α-series. One is steric in origin and involves interactions of the angular methyl group with some of the axial hydrogen atoms, position 6 being the most likely candidate.[1] This apparently is more serious in a Δ^3- than in a Δ^2-enol, thus rationalizing the exclusive formation [1,2] of the Δ^2-enol acetate in 3-oxo-steroids (I), while over 30% of the Δ^3-isomer can be produced in the absence of the angular methyl group (IV).[5] The second factor is a hyperconjugative one associated with the presence of a methyl group and explains why a 2α-methyl-19-nor-3-oxo-steroid (III) again yields [5] only the Δ^2-enol in contrast to the mixture of Δ^2- and Δ^3-enol acetates observed [5] with (IV). The same explanation fits also the picture observed with 4α-methyl-3-oxo-steroids (VI), hyperconjugative stabilization of the 3,4-double bond apparently being responsible for the shift in isomer ratio observed in the presence of such a 4α-methyl group. It is pertinent that the present semiquantitative results are consistent for each pair of 3-oxo-/19-nor-3-oxo-steroids, the latter always containing about 30% more of the Δ^3-enol owing to relief of non-bonded interactions involved with the angular methyl group.

Experimental

M. p.s were determined on a Fisher–Johns block. Unless noted otherwise, rotations and infrared spectra were measured for chloroform and ultraviolet absorption spectra for ethanol solutions. We are indebted to Dr. J. Mathews and his staff for these determinations and for the optical rotatory dispersion curves (which were obtained with an automatically recording Rudolph spectropolarimeter).

17β-*Hydroxy*-4α-*methyl*-19-*nor*-5α-*androstan*-3-*one* (VIa).—4-Methyl-19-nortestosterone [7] (3·88 g.) in dioxan (50 c.c.) and ether (50 c.c.) was added with stirring in 1 min. to a solution of lithium (0·4 g.) in liquid ammonia (300 c.c.). The blue colour was discharged by addition of solid ammonium chloride (3 g.) and, after the ammonia had evaporated overnight, water was added and the product isolated with benzene. Chromatography on neutral alumina (200 g.) afforded, in the benzene eluates, the *product* (VIa) (3·24 g.), m. p. 155—159°; a sample, crystallized from heptane–ethyl acetate, had m. p. 161—163°, $\nu_{max.}$ (in KBr) 3390 and 1703 cm.$^{-1}$, $[\alpha]_D$ +34°, no selective ultraviolet absorption in the 250 mμ region, R.D. in MeOH (*c* 0·065) $[\alpha]_{589}$ +29°, $[\alpha]_{305}$ +1050°, $[\alpha]_{270}$ −1075° (Found: C, 78·5; H, 10·3. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%).

Enol Acetylation of 17β-*Hydroxy*-4α-*methyl*-19-*nor*-5α-*androstan*-3-*one* (VIa).—(a) *With acetic anhydride–perchloric acid.* An ice-cold mixture of acetic anhydride (3 c.c.) and 72% perchloric acid (5 drops) was added to the ketone (VIa) (0·5 g.) in benzene (40 c.c.) and carbon tetrachloride (15 c.c.). After 4 hr. at room temperature ice–water was added followed by more carbon tetrachloride, the mixture was washed with sodium hydrogen carbonate and water, and the solvent was removed. Nuclear magnetic resonance analysis of the total crude acetate (m. p. 170—173°) indicated the predominance of 3,17β-*diacetoxy*-4-*methyl*-5α-*androst*-3-*ene* (VIIa) with no more than 5% of the Δ^2-acetate (VIIIa). Recrystallization from methanol provided a specimen (0·4 g.), m. p. 183—185°, $\nu_{max.}$ 1735 (sh), 1722 and 1240 cm.$^{-1}$, $[\alpha]_D$ −54° (*c* 0·28) (Found: C, 74·1; H, 9·0. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%).

(b) *With isopropenyl acetate.* The ketone (VIa) (2·21 g.), toluene-*p*-sulphonic acid monohydrate (0·15 g.), and isopropenyl acetate (100 c.c.) were heated under reflux for 6 hr. and most

of the isopropenyl acetate was then distilled off in 2 hr. The product was isolated with ethyl acetate and recrystallized once from hexane, to afford an acetate mixture (1·89 g.), m. p. 120—135°, which according to nuclear magnetic resonance analysis consisted of approximately equal amounts of the Δ^2- (VIIIa) and Δ^3-acetate (VIIa). For analysis a sample was passed through neutral alumina (activity VI) in hexane–benzene (4 : 1); it had m. p. 160—167°, $[\alpha]_D$ −24·5° (*c* 0·24) (Found: C, 73·4; H, 9·2%).

Bromination of Above Enol Acetates.—(*a*) Bromine (0·77 g.) in buffer solution [4] (75 c.c.) (2·0 g. of sodium acetate in 160 c.c. of glacial acetic acid and 40 c.c. of carbon tetrachloride) was added in 20 min. to the crude enol acetate (1·81 g.) from the perchloric acid-catalyzed enol acetylation in 75 c.c. of buffer solution. After the mixture had been stirred for an additional 15 min., chloroform was added and the mixture washed successively with water, aqueous sodium hydrogen carbonate, and water, dried, and evaporated. The total crude crystalline bromo-ketone had $\lambda_{max.}$ 302 mμ (log ε 2·13) and a negative Cotton effect with trough at $[\alpha]_{330}$ −2285°. Partition chromatography on Celite (150 g.) impregnated with dimethylformamide (75 c.c.) and elution with hexane saturated with dimethylformamide provided 17β-*acetoxy*-4β-*bromo*-4α-*methyl*-19-*nor*-5α-*androstan*-3-*one* (IXa) (1·7 g.), m. p. 131—141°; a specimen recrystallised from ethanol had m. p. 148° (decomp.), $\lambda_{max.}$ 306 mμ (log ε 2·06), R.D. in MeOH (*c* 0·075) $[\alpha]_{589}$ −42°, $[\alpha]_{332·5}$ −2555°, $[\alpha]_{315}$ −872° (Found: C, 61·8; H, 7·7; Br, 20·2. $C_{21}H_{31}BrO_3$ requires C, 61·3; H, 7·6; Br, 19·4%).

The crude bromo-ketone (0·47 g.) (before chromatography) was heated under reflux for 5·5 hr. with lithium carbonate (1·2 g.) and lithium bromide (1·2 g.) in dimethylformamide [14] (10 c.c.), yielding yellow crystals (0·37 g.) whose ultraviolet absorption spectrum ($\lambda_{max.}$ 249 mμ, log ε 4·06) indicated the virtual absence of the Δ^1-isomer (XIIa). Recrystallization from heptane led to 4-methyl-19-nortestosterone acetate [7,21] (Xa), m. p. 122—124°, $\lambda_{max.}$ 249 mμ (log ε 4·16).

(*b*) Similar bromination of the crude enol acetate mixture (VIIa and VIIIa) (1·55 g.) arising from the isopropenyl acetate acetylation afforded a yellow amorphous residue consisting of compounds (IXa and XIa) ($\lambda_{max.}$ 303 mμ, log ε 2·06; positive Cotton effect in methanol with peak at $[\alpha]_{330}$ +420°) which could not be separated by chromatography. It was therefore dehydrobrominated with lithium bromide–lithium carbonate, as described under (*a*), giving a mixture (1·1 g.) of Δ^1- (XIIa) and Δ^4-ketones (Xa) as demonstrated by the ultraviolet absorption maximum at 238 mμ. Chromatography on neutral alumina (350 g.) and spectrophotometric examination of the various eluates yielded first the Δ^1-ketone (469 mg.) ($\lambda_{max.}$ 229—230 mμ) followed by an intermediate fraction ($\lambda_{max.}$ 234—245 mμ) and finally the Δ^4-ketone (Xa) (379 mg.) ($\lambda_{max.}$ above 247 mμ). One single recrystallization from heptane provided pure 4-*methyl*-19-*nortestosterone acetate* [7,21] (Xa), m. p. 122—124°, $\lambda_{max.}$ 249 mμ (log ε 4·16).

Recrystallization (from ethanol) of the pooled fractions with $\lambda_{max.}$ 229—230 mμ gave 17β-*acetoxy*-4α-*methyl*-19-*nor*-5α-*androst*-1-*en*-3-*one* (XIIa), m. p. 180—182°, $\nu_{max.}$ (in KBr) 1739, 1682, 1644, and 1252 cm.$^{-1}$, $[\alpha]_D$ +76° (*c* 0·24) (Found: C, 75·8; H, 9·1. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·15%).

17β-*Hydroxy*-4α-*methyl*-5α-*androstan*-3-*one* (VIb).—Reduction of 4-methyltestosterone [7,18] (8·5 g.) with lithium–ammonia was conducted as described above for the 19-nor-series and afforded *compound* (VIb) (6·8 g.), m. p. 201—208°. A sample crystallized from acetone had m. p. 208—209°, $\nu_{max.}$ (in KBr) 3560 and 1715 cm.$^{-1}$, $[\alpha]_D$ +32° (*c* 0·26), R.D. in MeOH (*c* 0·057) $[\alpha]_{589}$ +58°, $[\alpha]_{302·5}$ +862°, $[\alpha]_{260}$ −918°, $[\alpha]_{245}$ −699° (Found: C, 78·7; H, 10·4; O, 10·3. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6; O, 10·5%).

Enol Acetylation of Compound (VIb).—(a) *With acetic anhydride–perchloric acid.* The enol acetylation of 4α-methyldihydrotestosterone (VIb) (2·5 g.) was performed in the same manner as in the 19-nor-series (VIa) to give a crude enol acetate (2·7 g.), m. p. 162—170°, $[\alpha]_D$ +2·3°. As indicated in the discussion section, nuclear magnetic resonance analysis indicated the presence of 10—20% of unchanged ketone (VIb) while the enol acetate consisted of a 7 : 3 mixture of (VIIb) and (VIIIb). Chromatography of a sample on neutral alumina followed by recrystallization from heptane afforded a specimen, in which the ketonic contaminant had virtually been removed (nuclear magnetic resonance), while the enol acetate composition remained essentially unchanged; this had m. p. 174—176°, $[\alpha]_D$ −5° (*c* 0·26) (Found: C, 73·9; H, 9·1. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

Kinetically controlled bromination of the crude enol acetate (1·05 g.; m. p. 162—170°)

[21] Hartman, Tomasewski, and Dreiding, *J. Amer. Chem. Soc.*, 1956, **78**, 5662.

afforded a reddish gum, which by consideration (see discussion) of its negative Cotton effect (trough in methanol at $[\alpha]_{322\cdot5}$ −1085°) can be calculated to consist of *ca.* 80% of 4β-bromo- (IXb) and 20% of 2α-bromo-ketone (XIII). Chromatography of this gum on silica gel followed by elution with ethyl acetate–benzene (1 : 49) and recrystallization from isopropyl alcohol gave 17β-*acetoxy*-4β-*bromo*-4α-*methyl*-5α-*androstan*-3-*one* (IXb), m. p. 124—128°, $\lambda_{max.}$ 308 mμ (log ε 1·96), $[\alpha]_D$ −104° (*c* 0·27), R.D. in MeOH (*c* 0·05) $[\alpha]_{589}$ −196°, $[\alpha]_{332\cdot5}$ −1870°, $[\alpha]_{285}$ +1665°, $[\alpha]_{250}$ +447° (Found: C, 62·4; H, 8·0; Br, 19·6. $C_{22}H_{33}BrO_3$ requires C, 62·1; H, 7·8; Br, 18·8%).

In a second experiment, the crude enol acetate (1·5 g.) was brominated and immediately dehydrobrominated (lithium carbonate–lithium bromide [14]). The dehydrobromination mixture was then chromatographed, the various fractions being pooled according to their ultraviolet absorption maximum. Recrystallization (from methanol) of 326 mg. of material with $\lambda_{max.}$ at 228—232 mμ followed by high-vacuum sublimation afforded pure 17β-*acetoxy*-4α-*methyl*-5α-*androst*-1-*en*-3-*one* (XIIb), m. p. 154—155°, $\lambda_{max.}$ 230 mμ (log ε 3·93), $\nu_{max.}$ (in KBr) 1730, 1690, and 1255 cm.$^{-1}$, $[\alpha]_D$ +20° (*c* 0·15) (Found: C, 76·8; H, 9·3; O, 14·2. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4; O, 13·9%).

The combined chromatogram fractions (388 mg.) with ultraviolet maxima between 246 and 250 mμ were recrystallized from heptane, to yield 4-*methyltestosterone acetate* (Xb), m. p. 163—164°, $\lambda_{max.}$ 250 mμ (log ε 4·19), $\nu_{max.}$ (in KBr) 1730, 1665, 1620, and 1250 cm.$^{-1}$, $[\alpha]_D$ +108° (*c* 0·31) (Found: C, 76·7; H, 9·4; O, 14·2. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4; O, 13·9%).

(b) *With isopropenyl acetate.* The enol acetylation of compound (VIb) (3·5 g.) with isopropenyl acetate was performed as described above and furnished a crude product (3·65 g.), m. p. 153—162°, which was shown by nuclear magnetic resonance analysis (see discussion) to contain nearly 50% of unchanged ketone. This could be removed by chromatography on alumina and recrystallization from hexane, whereupon an enol acetate mixture was secured in which the ratio of (VIIIb) to (VIIb) was ~3 : 1 (see discussion); it had m. p. 188—191°, $[\alpha]_D$ −8·5° (*c* 0·44) (Found: C, 73·6; H, 9·0. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

Quantitative evaluation of the composition of the kinetically controlled bromination product of the above crude enol acetylation mixture (m. p. 153—162°) by rotatory dispersion proved to be too complicated because of admixture with unchanged ketone (VIb) which consumes only little bromine in the presence of sodium acetate. However, chromatography of the bromination product on silica gel, followed by elution with ethyl acetate–benzene (3 : 97) and recrystallisation from isopropyl alcohol, led to 17β-*acetoxy*-2α-*bromo*-4α-*methyl*-5α-*androstan*-3-*one* (XIII), m. p. 174° (decomp.), $\lambda_{max.}$ 280 mμ (log ε 1·43), $[\alpha]_D$ +12° (*c* 0·32), R.D. in MeOH (*c* 0·049) $[\alpha]_{307\cdot5}$ +736°, $[\alpha]_{240}$ −1015° (Found: C, 62·1; H, 7·75; Br, 19·1. $C_{22}H_{33}BrO_3$ requires C, 62·1; H, 7·8; Br, 18·8%).

Dehydrobromination of the pure acetate (XIII) (15 mg.) by the lithium bromide procedure yielded a crude crystalline residue whose ultraviolet maximum at 229 mμ showed that it consisted of the Δ^1-ketone (XIIb) uncontaminated by its Δ^4-isomer (Xb).

Since the rotatory dispersion curves of the two pure possible bromination products (IXb derived from VIIb and XIII derived from VIIIb) of the enol acetate mixture were now available, a 40 mg. sample of the above purified enol acetate (m. p. 188—191°; 3 pt. of VIIIb and 1 pt. of VIIb, see above) was subjected to kinetically controlled bromination. The resulting total crude bromination product (m. p. 132—138°) had a positive Cotton effect with $[\alpha]_{305}$ +510° and as the 4β-bromo-ketone (IXb) has $[\alpha]_{305}$ 0°, one can conclude from the bromination experiment that the purified enol acetate consisted of 70% of (VIIIb) and 30% of (VIIb), in excellent agreement with the nuclear magnetic resonance results.

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