SYNTHESIS OF (19*E*)-17β-HYDROXY-3-OXOANDROST-4-EN-19-AL 19-(O-CARBOXYMETHYL)OXIME*

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The title compound *XIII* was synthesized from epoxide *I*. Cleavage with zinc dust and Jones' oxidation under mild conditions afforded aldehyde *V*. Reaction with (O-carboxymethyl)hydroxylamine hemihydrochloride followed by methylation with diazomethane led to oxime *X* which on partial hydrolysis gave the 3-hydroxy derivative *VIII*. Its oxidation accompanied with a rearrangement of the double bond yielded ketone *XVI* which on hydrolysis afforded the desired hapten *XIII*.

Antibodies with low cross-reactivity with 5α-dihydrotestosterone (DHT) are of interest for immunoanalytical determination of testosterone. Several authors have studied such derivatives linked to various carbons of the steroid molecule. The lowest cross-reactivity with DHT showed C-15 (2·8%; cf. ref.[1]), C-17 (5%; cf. ref.[2]) and, especially, C-19 (0·78%; cf. ref.[3]) substituted derivatives.

This observation, and a need for more specific antisera for use in radioimmunoassays of steroids, prompted us to develop a synthesis of a new type of easily accessible immunogens. In this paper we describe the synthesis of the 19-(O-carboxymethyl)oxime derivative of testosterone *XIII* as the first representative of this group.

The originally considered route for synthesis of the acid *XIII* started with the known[4] acetate-benzoate *II*. The cleavage of the epoxide ring was performed in a tert-butanol–water mixture (3 : 2) with zinc dust. This modification of a well known reaction affords 19-hydroxyderivative *IV* in an almost quantitative yield. Oxidation to aldehyde *VI* (cf. ref.[5]) was carried out at low temperature with Jones' reagent; under these conditions no carboxyl containing product was detected. Oximation of the 19-oxogroup was carried out under standard conditions with (O-carboxymethyl)hydroxylamine hemihydrochloride in pyridine to yield, after methylation of the carboxyl group with diazomethane, the 19-O-carboxymethyl-

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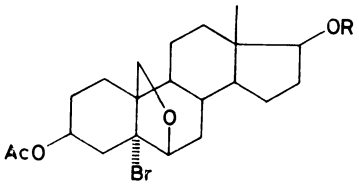
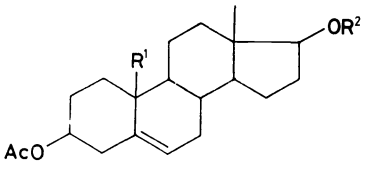
oxime methylester *XII*. This structure is well confirmed by the ^{1}H NMR spectrum (see Table I). The corresponding signals prove safely the presence of the –CH=N—O—CH_2COOCH_3 grouping at C-10. The *E*-configuration of the oxime moiety follows from the chemical shift of the H-19 proton (δ = 7·42, cf. ref.[6]).

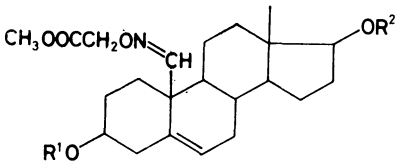
Partial hydrolysis of the acetate group with methanolic hydrochloric acid led to alcohol *XI* in which the presence of the newly formed hydroxyl group and the presence of the remaining benzoyloxy group is proved by its IR spectrum (bands of hydroxyl group 3 615 and 3 520 cm^{-1}) and signals of the benzoate moiety in ^{1}H NMR spectrum (Table I). Oppenauer oxidaion as well as Jones' oxidation followed by treatment with oxalic acid afforded ketone *XVII*. However, attempts to hydrolyse this ester benzoate to the desired acid-alcohol *XIII* were unsuccessful. Under mild conditions only the methyl ester group was hydrolysed and the benzoate *XIV* was formed as the sole product. Methylation with diazomethane afforded the starting methylester-benzoate *XVII*, thus proving the proposed structure *XIV* for the product of hydrolysis without any doubt. More efficient conditions necessary to hydrolyse also the 17-benzoyloxy group casued decomposition of the ketone-oxime grouping in ring A.



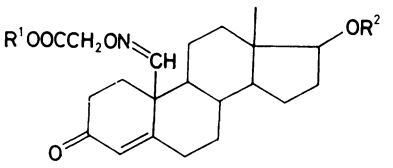
I, R = Ac
II, R = Bz



III, R^1= CH_2OH ; R^2= Ac
IV, R^1= CH_2OH ; R^2= Bz
V, R^1= CHO ; R^2= Ac
VI, R^1= CHO ; R^2= Bz



VII, R^1= R^2= H
VIII, R^1= H ; R^2= Ac
IX, R^1= Ac ; R^2= H
X, R^1= R^2= Ac
XI, R^1= H ; R^2= Bz
XII, R^1= Ac ; R^2= Bz



XIII, R^1= R^2= H
XIV, R^1= H ; R^2= Bz
XV, R^1= CH_3, R^2= H
XVI, R^1= CH_3 ; R^2= Ac
XVII, R^1= CH_3 ; R^2= Bz

Ac = $OCCH_3$; Bz = OCC_6H_5

We therefore followed an alternative route starting from the known[7] epoxide-diacetate *I*. Cleavage of the epoxide ring led to alcohol *III* (cf. ref.[8]) which on oxidation gave aldehyde *V* (cf. ref.[9]). Oximation and methylation under similar conditions as described above led to oxime diacetate *X* which was submitted to partial hydrolysis with methanolic hydrochloric acid. All the three expected products of hydrolysis (*VII*, *VIII*, and *IX*) were formed, but the desired monoacetate *VIII* represented the main component in the reaction mixture, containing also some unreacted starting diacetate *X*. All four components were easily separated by column chromatography. The structure of the two monoacetates were established as follows: benzoylation of the minor product yielded the diester *XII* proving securely the structure *IX* for this compound. The structure of the desired monoacetate *VIII* follows from the spectral evidence: the presence of the hydroxyl group is shown by the IR spectrum (bands at 3 615 and 3 510 cm^{-1}). Further evidence arises from the ^1H NMR spectrum which proves the presence of one single acetoxy group as well as its localization: the multiplet of H-3α at $\delta = 3{\cdot}54$ ($W \approx 36$ Hz) points to the position of the hydroxyl group at C-3. Oxidation of alcohol *VIII* with Jones' reagent followed by treatment with oxalic acid yielded the ketone *XVI* which on hydrolysis with methanolic hydrochloric acid gave the 17-hydroxy derivative *XV*. This compound was also conventionally prepared directly from the oxidation product *XVI* by treatment with

TABLE I

^1H NMR spectral parameters of (19-O-carboxymethyl)oxime derivatives[a]

Compound	H-18 (3 H)	H-19 (1 H)	H-3α (1 H)	H-17α (1 H)	H-4 (1 H)	H-6 (1 H)	OCH_2CO (2 H)	$COOCH_3$ (3 H)
VIII[b]	0·78 s	7·38 s	3·54 m[c]	[d]	[e]	5·59 bd[f]	4·62 s	3·76 s
X[g]	0·78 s	7·40 s	[d]	[d]	[e]	5·64 bd[f]	4·63 s	3·76 s
XI[h]	0·93 s	7·41 s	3·57 m[c]	4·86 bt[i]	[e]	5·62 bd[f]	4·63 s	3·76 s
XII[j]	0·93 s	7·42 s	[d]	4·85 bt[i]	[e]	5·64 bd[f]	4·64 s	3·77 s
XIII[k]	0·65 s	7·76 s	—	[e]	5·79 bs	[e]	4·52 s	—
XVI[l,m]	0·83 s	7·66 s	—	4·60 dd[n]	5·83 d[o]	[e]	4·61 s	3·75 s
XVII[h]	0·97 s	7·68 s	—	4·87 bt[i]	5·88 bs	[e]	4·61 s	3·75 s

[a] Measured on Tesla BS-476 instrument (100 MHz, FT mode) in deuteriochloroform with tetramethylsilane as internal standard; [b] other signal 2·03 s, 3 H (CH_3COO); [c] $W \approx 36$; [d] overlapped with singlet of OCH_2COO group; [e] undeterminable value; [f] $J \approx 4{\cdot}5$; [g] other signals 2·01 s and 2·03 s, 2 × 3 H (2 × CH_3COO); [h] other signals 7·45 m, 3 H and 8·02 m, 2 H (C_6H_5COO); [i] $J \approx 8$; [j] other signals 2·01 s, 3 H (CH_3COO); 7·45 m, 3 H and 8·02 m, 2 H (C_6H_5COO); [k] measured in CD_3SOCD_3; [l] measured on Varian XL-200 instrument (200 MHz, FT mode); [m] other signal 2·04 s, 3 H (CH_3COO); [n] $J(17\alpha,16\alpha) = 7{\cdot}6$, $J(17\alpha,16\beta) = 9{\cdot}2$; [o] $J(4,2\beta) = 1{\cdot}8$.

methanolic hydrochloric acid. Next to the ^{1}H NMR spectral evidence (see Table I) the structure of the alcohol *XV* follows also from its mass spectrum. It exhibits the molecular ion at *m/z* 389 and a peak at *m/z* 300 which was formed by the loss of OCH_2COOCH_3 (*m/z* 89) from the molecular ion. Analogous fragmentation was observed in compounds *VII*, *X*, *XI*, *XII*, *XVI* and *XVII* carrying the —CH=NOCH$_2$. .COOCH$_3$ grouping at the 10β position. Mild alkaline hydrolysis of *XV* afforded the required acid *XIII*. Spectral evidence is in agreement with this expected structure. In the IR spectrum the hydroxyl group is represented by the band at 3 615 cm^{-1}, the carboxyl group by a broad band at 3 500 – 2 500 and a band at 1 730 cm^{-1} and the conjugated system in the A ring by the bands at 1 675 and 1 625 cm^{-1}. In the ^{1}H NMR spectrum the H-19 appears as a singlet at δ = 7·76, H-4 as a broad singlet at δ = 5·79 and the methylene group of the OCH_2COO grouping as a singlet at δ = 4·52 (see Table I).

The antigenic properties of antibodies of this new hapten will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical rotations were carried out in chloroform with an error of ±2° at 23°C. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in chloroform; wavenumbers are given in cm^{-1}. ^{1}H NMR spectra was measured on a Tesla BS-476 instrument (100 MHz, FT mode) in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) and widths (*W*) in Hz. All data were obtained by first order analysis. Mass spectra were recorded on a VG Analytical ZAB-EQ spectrometer (energy of ionizing electrons 70 eV, ion source temperature 170–200°C). The identity of samples prepared by different procedures was checked by thin-layer chromatography (TLC, silica gel G Woelm, detection with sulfuric acid) and by infrared spectra. Working up of a reaction mixture in the "usual way" means extraction of the product with an organic solvent and washing the extract with 5% aqueous hydrochloric acid, water, 5% aqueous sodium hydrogen carbonate, water, drying over magnesium sulate, and evaporation of the solvent in vacuo at 50°C.

19-Hydroxyandrost-5-ene-3β,17β-diyl Diacetate (*III*)

The epoxide[7] *I* (13·0 g, 27·7 mmol) was dissolved in 2-methyl-2-propanol (300 ml) and water (200 ml), zinc dust (91·5 g, 1·4 mol) was added and the reaction mixture was refluxed under efficient stirring for 1 h. After cooling off the metal was removed by filtration, washed with ethanol and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was worked up as usual. After evaporation of the solvent the residue was crystallized from chloroform–ligroin to yield 9·1 g (84%) of the diacetate *III*, m.p. 149–150°C, $[\alpha]_D$ −59° (*c* 2·3), in agreement with the literature[8] (m.p. 150–151°C, $[\alpha]_D$ −59°).

19-Hydroxyandrost-5-ene-3β,17β-diyl 3-Acetate 17-Benzoate (*IV*)

The epoxide[4] *II* (5·0 g, 9·4 mmol) was suspended in 2-methyl-2-propanol (120 ml) and water (8·0 ml) and treated with zinc dust (35·3 g, 0·54 mol) as described in the previous experiment. Similar working up and crystallization from ether–ligroin gave 3·8 g (88%) of the benzoate *IV*,

m.p. 143–144°C, $[\alpha]_D$ +3° (*c* 2·8). IR spectrum: 3 620, 3 570 (OH); 1 716 (C=O); 1 650 (C=C); 1 602, 1 582 (arom.); 1 280, 1 256 (C–O). ^{1}H NMR spectrum: 8·03 m, 2 H and 7·56 m, 3 H (C_6H_5COO); 5·78 bd, 1 H (H-6, J = 4·5); 4·85 bt, 1 H (H-17, J = 8); 4·66 m, 1 H (H-3); 3·87 and 3·60, AB system (2 × H-19, J(A, B) = 11·5); 2·03 s, 3 H (CH_3COO); 1·01 s, 3 H (3 × H-18). For $C_{28}H_{36}O_5$ (452·6) calculated: 74·31% C, 8·02% H; found: 74·15% C, 7·95% H.

19-Oxoandrost-5-ene-3β,17β-diyl Diacetate (*V*)

The alcohol *III* (9·0 g, 23 mmol) in acetone (100 ml) was treated at +5°C with Jones' reagent and allowed to stand at this temperature for 4 min. Methanol (5 ml) was added and the reaction mixture was allowed to stand at room temperature for 10 min to remove the excess oxidizing agent. The product was precipitated with water and collected by suction. The crystals were dissolved in ethyl acetate and the solution was worked up in the usual way. The residue after evaporation of the solvent was crystallized from heptane to afford 7·8 g (87%) of the aldehyde *V*, m.p. 147–149°C, $[\alpha]_D$ −248° (*c* 1·8) in agreement with the literature[9] (m.p. 150–153°C, $[\alpha]_D$ −252°).

19-Oxoandrost-5-ene-3β,17β-diyl 3-Acetate 17-Benzoate (*VI*)

The alcohol *IV* (4·5 g, 9·9 mmol) was oxidized with Jones' reagent in acetone (80 ml) as described in the previous experiment. Crysallization from methanol yielded 3·1 g (69%) of the aldehyde *VI*, m.p. 139–140°C, $[\alpha]_D$ −172° (*c* 2·3). Literature[5] gives m.p. 129–131°C, $[\alpha]_D$ −162°. For $C_{28}H_{34}O_5$ (450·6) calculated: 74·64% C, 7·61% H; found: 74·42% C, 7·53% H.

(19*E*)-3β,17β-Dihydroxyandrost-5-en-19-al 19-(O-Carboxymethyl)oxime Methylester (*VII*)

The diacetate *X* (8·0 g, 16·8 mmol) in chloroform (30 ml) was treated with a solution of conc. hydrochloric acid (5 ml, 60 mmol) in methanol (200 ml) and allowed to stand at 18°C for 2·5 h. The reaction mixture was poured into a 5% sodium hydrogen carbonate solution (600 ml), the product was taken into ethyl acetate and the extract was worked up. The residue after evaporation of the solvent consisted of four components according to increasing polarity (TLC): the starting diacetate *X*, the monoacetates *VIII* an *IX* and the diol *VII*. It was chromatographed over silica gel (400 g) in ether–benzene (1 : 9). Fractions with the most polar product were worked up and the solid residue after evaporation of the solvents was crystallized from chloroform–ligroin to yield 900 mg (14%) of the diol *VII*, m.p. 162–163°C, $[\alpha]_D$ −136° (*c* 2·4). For $C_{22}H_{33}NO_5$ (391·5) calculated: 67·49% C, 8·50% H, 3·58% N; found; 67·35% C, 8·29% H, 3·49% N.

(19*E*)-3β-Hydroxy-19-oxoandrost-5-en-17β-yl Acetate
19-(O-Carboxymethyl)oxime Methylester (*VIII*)

Fractions containing the monoacetate *VIII* (see the preceding experiment) were combined and evaporated. Crystallization from methanol gave 3·6 g (50%) of the monoacetate *VIII*, m.p. 71–72°C, $[\alpha]_D$ −137° (*c* 2·6). IR spectrum: 3 615, 3 510 (O–H); 1 745 sh, 1 723 (C=O); 1 252 (C–O acetate). Mass spectrum, *m/z*: 433 (M^+), 415 (M − H_2O), 360, 344 (M − OCH_2COOCH_3), 326 (M − H_2O − OCH_2COOCH_3). For $C_{24}H_{35}NO_6$ (433·5) calculated: 66·49% C, 8·14% H, 3·23% N; found: 66·37% C, 8·06% H, 3·14% N.

(19*E*)-17β-Hydroxy-19-oxoandrost-5-en-3β-yl Acetate
19-(O-Carboxymethyl)oxime Methylester (*IX*)

Fractions containing the monoacetate *IX* (see above) were combined and evaporated. Crystalliza-

tion from methanol gave 420 mg (6%) of the monoacetate *IX*, m.p. 116–117°C, $[\alpha]_D$ −138° (*c* 2·1). For $C_{24}H_{35}NO_6$ (433·5) calculated: 66·49% C, 8·14% H, 3·23% N; found: 66·41% C, 7·95% H, 3·05% N.

(19*E*)-19-Oxoandrost-5-ene-3β,17β-diyl Diacetate
19-(O-Carboxymethyl)oxime Methylester (*X*)

The aldehyde *V* (25·0 g, 64·4 mmol) in pyridine (240 ml) was treated with (O-carboxymethyl)-hydroxylamine hemihydrochloride (15·0 g, 137·2 mmol) and allowed to stand at room temperature for 18 h. The reaction mixture was decomposed with ice and conc. hydrochloric acid (320 ml) and the product was taken into ethyl acetate. The solution was washed repeatedly with water, dried over magnesium sulfate and the solvent was distilled off. The residue was dissolved in methanol (20 ml) and ether (400 ml) and treated with diazomethane in ether. Excess diazomethane was removed with acetic acid, the solution was diluted with ethyl acetate and worked up. Crystallization from methanol afforded 24·0 g (78%) of the oxime *X*, m.p. 109–110°C, $[\alpha]_D$ −143° (*c* 3·1). IR spectrum: 1 745 sh, 1 722 (C=O); 1 252 (C–O acetate). Mass spectrum, *m/z*: 475 (M^+), 415 (M − CH_3COOH), 326 (M − CH_3COOH − OCH_2COOCH_3). For $C_{26}H_{37}$·NO_7 (475·6) calculated: 65·66% C, 7·84% H, 2·95% N; found: 65·48% C, 7·62% H, 2·82% N.

(19*E*)-3β-Hydroxy-19-oxoandrost-5-en-17β-yl Benzoate
19-(O-Carboxymethyl)oxime Methylester (*XI*)

The acetate *XII* (3·0 g, 5·6 mmol) in chloroform (40 ml) was treated with a solution of conc. hydrochloric acid (5·0 ml, 60 mmol) in methanol (150 ml) and allowed to stand at 35°C for 20 h. The reaction mixture was poured into 5% sodium hydrogen carbonate solution (200 ml) and the product was extracted with ethyl acetate. Usual working up and crystallization from ether–ligroin afforded 2·05 g (74%) of the alcohol *XI*, m.p. 116–117°C, $[\alpha]_D$ −104° (*c* 2·9). IR spectrum: 3 615, 3 520 (O–H); 1 752 (COOR); 1 711, 1 280 (benzoate); 1 602, 1 582, 1 482 (arom.). Mass spectrum, *m/z*: 495 (M^+), 406 (M − OCH_2COOCH_3), 388 (M − H_2O − OCH_2COOCH_3). For $C_{29}H_{37}NO_6$ (495·6) calculated: 70·28% C, 7·52% H, 2·83% N; found: 70·15% C, 7·42% H, 2·77% N.

(19*E*)-19-Oxoandrost-5-ene-3β,17β-diyl 3-Acetate 17-Benzoate
19-(O-Carboxymethyl)oxime Methylester (*XII*)

a) The aldehyde *VI* (3·0 g, 6·7 mmol) in pyridine (30 ml) was treated with (O-carboxymethyl)-hydroxylamine hemihydrochloride (2·3 g, 21·0 mmol) and allowed to stand at room temperature for 18 h. The reaction mixture was decomposed with ice and conc. hydrochloric acid (40 ml) and the product was isolated with ethyl acetate. The extract was washed with water to neutrality, dried over magnesium sulfate and the solvent was distilled off in vacuo. The residue was dissolved in methanol (5 ml) and ether (100 ml) and treated with ethereal solution of diazomethane. Excess diazomethane was removed with acetic acid, the reaction mixture was diluted with ethyl acetate and the solution was worked up. Crystallization from ether–ligroin yielded 2·9 g (81%) of the oxime *XII*, m.p. 96–97°C, $[\alpha]_D$ −115° (*c* 2·3). IR spectrum: 1 745 sh, 1 722 (C=O); 1 602, 1 582, 1 482 (arom.); 1 281 (C–O benzoate); 1 256 (C–O acetate). Mass spectrum, *m/z*: 537 (M^+), 477 (M − CH_3COOH), 388 (M − CH_3COOH − OCH_2COOCH_3). For $C_{31}H_{39}$·NO_7 (537·6) calculated: 69·25% C, 7·31% H, 2·61% N; found: 69·11% C, 7·26% H, 2·52% N.

b) The alcohol *IX* (1·8 g, 3·6 mmol) in pyridine (10 ml) was treated with benzoylchloride (2·0 ml, 17·2 mmol) and allowed to stand at room temperature for 18 h. The reaction mixture

was decomposed with ice and water and the product was isolated with ethyl acetate. Working up and crystallization from ether–ligroin yielded 1·48 g (66%) of the benzoate *XII*, m.p. 95–96°C, $[\alpha]_D$ −112° (*c* 1·8).

(19*E*)-17β-Hydroxy-3-oxoandrost-4-en-19-al 19-(O-Carboxymethyl)oxime (*XIII*)

The methylester *XV* (2·0 g, 5·1 mmol) in methanol (100 ml) was treated at 10°C under stirring and in argon atmosphere dropwise with a solution of potassium hydroxide (500 mg, 8·9 mmol) in water (100 ml). The hyrolysis was complete (TLC) after 3 h when 82 ml of the alkali were consumed. The reaction mixture was neutralized with hydrochloric acid, methanol was distilled off in vacuo and the residue was acidified with hydrochloric acid. The product was taken into ethyl acetate, the acid was extracted into a 7% sodium hydrogen carbonate solution (50 ml) and this solution of the sodium salt was washed thoroughly with ethyl acetate. After acidification with hydrochloric acid the product was extracted with ethyl acetate and the extract was washed with water to neutrality. The solvent was removed to a volume of about 5 ml and 30 ml of ether were added. After 20 h at 0°C the crystals were collected. Yield 1·65 g (86%) of the acid *XIII*, m.p. 166–167°C, $[\alpha]_D$ +127° (*c* 2·3). IR spectrum: 3 615 (O–H); 3 500–2 500, 1 730 (COOH); 1 675, 1 625 (C=C–C=O). For $C_{21}H_{29}NO_5$ (375·5) calculated: 67·18% C, 7·79% H, 3·73% N; found: 66·95% C, 7·63% H, 3·62% N.

(19*E*)-3,19-Dioxoandrost-4-en-17β-yl Benzoate 19-(O-Carboxymethyl)oxime (*XIV*)

The ester *XVII* (1·0 g, 2·0 mmol) was hydrolyzed as described in the previous experiment. Similar working up and crystallization from benzene–ligroin afforded 720 mg (74%) of the acid *XIV*, m.p. 192–193°C, $[\alpha]_D$ +135° (*c* 2·7). For $C_{28}H_{33}NO_6$ (479·5) calculated: 70·13% C, 6·94% H, 2·92% N; found: 69·87% C, 6·81% H, 2·87% N.

(19*E*)-17β-Hydroxy-3-oxoandrost-4-en-19-al 19-(O-Carboxymethyl)oxime Methylester (*XV*)

a) The acetate *XVI* (5·0 g, 11·6 mmol) in chloroform (4 ml) was treated with a solution of conc. hydrochloric acid (1·5 ml, 18 mmol) in methanol (60 ml) and allowed to stand at 30°C for 18 h. The reaction mixture was poured into 5% sodium hydrogen carbonate solution (150 ml) and the product taken into ethyl acetate. Working up afforded a crude product which was chromatographed over silica gel (220 g) in ether–benzene (1 : 4). Crystallization from ether–ligroin gave 3·85 g (85%) of the alcohol *XV*, m.p. 59–60°C, $[\alpha]_D$ +151° (*c* 2·2). Mass spectrum, *m/z*: 389 (M^+), 300 ($M - OCH_2COOCH_3$). For $C_{22}H_{31}NO_5$ (389·5) calculated: 67·84% C, 8·02% H, 3·60% N; found: 67·65% C, 7·97% H, 3·54% N.

b) The acid *XIII* (500 mg, 1·3 mmol) in methanol (5 ml) and ether (50 ml) was treated with a solution of diazomethane in ether. Excess diazomethane was removed with acetic acid, the solution was diluted with ethyl acetate and washed with 5% sodium hydrogen carbonate. Working up and crystallization from ether–ligroin yielded 410 mg (80%) of the ester *XV*, m.p. 58–60°C, $[\alpha]_D$ +148° (*c* 2·6).

c) The alcohol *VIII* (6·0 g, 13·8 mmol) in acetone (100 ml) was treated with excess Jones' reagent. After 5 min at room temperature the excess reagent was removed with methanol, water was added and the product was extracted with ethyl acetate. Working up and evaporation of the solvent yielded a crystalline residue (6·0 g) which was dissolved in chloroform (4 ml) and treated with a solution of conc. hydrochloric acid (1·5 ml, 18 mmol) in methanol. After 18 h at 30°C the reaction mixture was poured into 5% sodium hydrogen carbonate and the product was

extracted with ethyl acetate. Working up, chromatography over silica gel (250 g) in ether–benzene (1 : 4) and crystallization from ether–ligroin gave 3·5 g (65%) of the ketone *XV*, m.p. 60—61°C, $[\alpha]_D$ +150° (*c* 2·4).

(19*E*)-3,19-Dioxoandrost-4-en-17β-yl Acetate
19-(O-Carboxymethyl)oxime Methylester (*XVI*)

The alcohol *VIII* (3·0 g, 6·9 mmol) in acetone (40 ml) was treated with excess Jones' reagent and worked up as described in the previous experiment. The crude oxidation product was dissolved in ethanol (25 ml), oxalic acid dihydrate (1·0 g, 7·9 mmol) was added and the mixture was heated to 60°C for 3 h. After cooling off the solution was diluted with ethyl acetate (300 ml), washed with 5% sodium hydrogen carbonate and water, dried over magnesium sulfate and the solvents were removed in vacuo. The residue was chromatographed over silica gel (150 g) in ether–benzene (1 : 9). Crystallization from ether–ligroin yielded 2·05 g (69%) of the ketone *XVI*, m.p. 115—117°C, $[\alpha]_D$ +117° (*c* 2·6). IR spectrum: 1 745 sh, 1 730 (C=O); 1 671, 1 623 (C=C—C=O); 1 260 (C–O acetate). Mass spectrum, *m/z*: 431 (M^+), 342 ($M - OCH_2COOCH_3$). For $C_{24}H_{33}NO_6$ (431·5) calculated: 66·80% C, 7·71% H, 3·25% N; found: 66·67% C, 7·58% H, 3·19% N.

(19*E*)-3,19-Dioxoandrost-4-en-17β-yl Benzoate
19-(O-Carboxymethyl)oxime Methylester (*XVII*)

a) The alcohol *XI* (4·0 g, 8·1 mmol) was oxidized with Jones' reagent and treated with oxalic acid as described in the previous experiment. Similar working up and chromatography over silica gel (200 g) in the same solvent mixture afforded after crystallization from chloroform–ligroin 2·8 g (70%) of the ketone *XVII*, m.p. 141—142°C, $[\alpha]_D$ +139° (*c* 2·7). IR spectrum: 1 751 (COOR); 1 712, 1 281 (benzoate); 1 670, 1 621 (C=C—C=O); 1 602, 1 582, 1 482 (arom.). Mass spectrum, *m/z*: 493 (M^+), 404 ($M - OCH_2COOCH_3$). For $C_{29}H_{35}NO_6$ (493·6) calculated: 70·57% C, 7·15% H, 2·84% N; found: 70·48% C, 7·03% H, 2·61% N.

b) The alcohol *XI* (4·0 g, 8·1 mmol) was dissolved in toluene (130 ml), cyclohexanone (15 ml, 145 mmol) and a solution of aluminum isopropoxide (2·0 g, 9·8 mmol) in toluene (15 ml) were added and refluxed for 1·5 h. After cooling off to room temperature the reaction mixture was decomposed with ice and 10% hydrochloric acid and the product was isolated with ethyl acetate. Working up afforded an oinly residue which was submitted to steam distillation to remove the voltiles components. The product was taken into ethyl acetate and the solution was worked up. Chromatography over silica gel (320 g) in ether–benzene (1 : 9) and crystallization from chloroform–ligroin gave 2·3 g (58%) of the ketone *XVII*, m.p. 142—143°C, $[\alpha]_D$ +135° (*c* 1·8).

c) The acid *XIV* (200 mg, 0·42 mmol) in methanol (1 ml) and ether (15 ml) was treated with ethereal diazomethane solution. Excess diazomethane was removed with acetic acid, ethyl acetate was added and the solution was worked up. The residue was crystallized from chloroform–ligroin to afford 165 mg (80%) of the methylester *XVII*, m.p. 140—141°C, $[\alpha]_D$ +138° (*c* 1·2).

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