SYNTHESES OF STEROID *O*-(3-CARBOXYPROPYL)OXIMES*

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The syntheses of *O*-(3-carboxypropyl)oxime derivatives, *i.e.* bis-homologues of *O*-(carboxymethyl)oxime derivatives (CMO), derived from dehydroepiandrosterone, testosterone and estradiol are presented. Both the reaction of steroid ketone with *O*-(3-carboxypropyl)hydroxylamine, and the reaction of sodium salt of steroid oxime with ethyl 4-bromobutyrate were alternatively evaluated, together with some other methods using successive chain lengthening. The compatibility with acetyl and methoxymethyl protecting groups was studied.
Key words: *O*-Alkylated oximes; *E/Z* Isomers.

O-(Carboxymethyl)oxime derivatives (CMOs) are routinely used[2] in preparation of steroid haptens for immunoassays. Recently, we described the synthesis[3,4] of their first homologues, *i.e. O*-(2-carboxyethyl)oximes (CEOs), of steroid hormones. In the case of 3-CEO derivatives of testosterone, the reduced susceptibility to the isomerization about the C=N double bond was proved, and these derivatives could be better chromatographically separated even in the form of conjugates with L-tyrosine[5]. Continuing this study, we focused our attention on the further lengthening of alkyl chain of the substituted oxime, *i.e.* to the insertion of methylene group between the oxime oxygen and terminal carboxyl in CEOs. The synthesis of these bis-homologues of CMO derivatives, *i.e. O*-(3-carboxypropyl)oxime derivatives (CPOs) of steroids, is the subject of the present study. Both the reaction of steroid ketone with *O*-(3-carboxypropyl)hydroxylamine and the reaction of sodium salt of steroid oxime with ethyl 4-bromobutyrate could be alternatively used for the synthesis of CPO derivatives. Carboxypropyl oximes derived from three steroid hormones were prepared: from dehydroepiandrosterone, testosterone and estradiol.

As the starting material for the synthesis of 17-CPO derivative of dehydroepiandrosterone **5**, 17-oxoandrost-5-en-3β-yl acetate (**1**) was used which gave single product **4**

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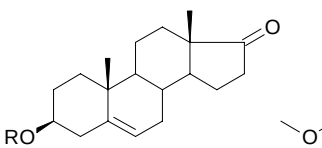
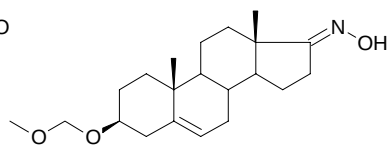
by the reaction with *O*-(3-carboxypropyl)hydroxylamine in pyridine. Its ^{1}H NMR spectrum contained triplet at δ 4.09 (J = 6.1 Hz) corresponding to the methylene group in $=NOCH_2$ and triplet of CH_2 group in the neighborhood of carboxyl at δ 2.47 (J = 7.3 Hz). The presence of $=NO(CH_2)_3COOH$ moiety in the molecule was proved also by the mass spectrometry. In the mass spectrum a base peak with *m/z* 268 was detected, which corresponded to the loss of $O(CH_2)_3COOH$ fragment and of a molecule of acetic acid from the molecular ion. In the IR spectrum bands of carboxyl OH (3 518 cm^{-1} monomer, 2 713 cm^{-1} assoc.) and of C=N double bond (1 650 cm^{-1}) were present. Alkaline hydrolysis of acetate **4** gave 17-CPO derivative **5**. Its ^{1}H NMR spectrum contained signal H-6 at δ 5.36, a methylene triplet at δ 4.05 (J = 6.1 Hz) from $=NOCH_2$, triplet of CH_2 group neighboring with carboxyl at δ 2.40 (J = 7.3 Hz), and a multiplet of H-3α at δ 3.50 (W = 31 Hz).



1, R = Ac
2, R = MOM



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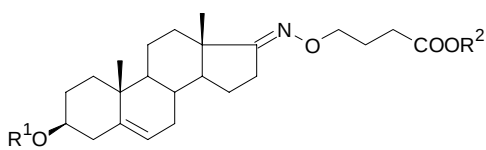


	R^1	R^2
4	Ac	H
5	H	H
6	MOM	CH_2CH_3
7	H	CH_3
8	MOM	H

Ac = Acetyl, MOM = Methoxymethyl

The second way, leading to the 17-CPO derivative **5**, used oxime of 3β-(methoxymethoxy)androst-5-en-17-one (**3**) as a starting compound. The sodium salt, prepared by the reaction with sodium hydride, was coupled with ethyl 4-bromobutyrate to give ethyl ester of 17-CPO derivative **6**. However, this reaction gave **6** only in low yield (13%); the unreacted oxime **3** was regenerated in 81% yield. The cleavage of the methoxymethyl (MOM) protecting group from compound **6** by concentrated hydrochloric acid in a methanol–benzene mixture was accompanied by transesterification and the methyl

ester **7** was isolated as a single product. In the ^{1}H NMR spectrum of **7** were besides a singlet of methyl ester at δ 3.68 again two characteristic triplets: $=NOCH_2$ at δ 4.04 (J = 6.1 Hz) and CH_2COO at δ 2.41 (J = 7.3 Hz). The mass spectrum contained a base peak with *m/z* 286, which originated by splitting of the $O(CH_2)_3COOCH_3$ fragment from the molecular ion.

Methyl ester of 17-CPO derivative **7** was also accessible from the 17-oxo derivative **2**. In the first step, reaction with *O*-(3-carboxypropyl)hydroxylamine in pyridine yielded 17-CPO derivative **8**. The cleavage of MOM group by concentrated hydrochloric acid in a methanol–benzene mixture with simultaneous esterification of carboxyl group gave then compound **7** which was hydrolyzed by alkali into 17-CPO derivative **5**.

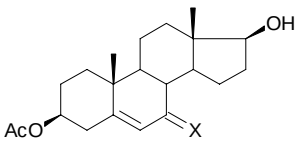
Further possibility of addition of four carbon synthon with terminal carboxyl to oxime was based on the reaction of the sodium salt of the oxime **3** with butano-4-lactone. However, even after 18 h heating to 90 °C this reagent gave no reaction and this approach was unsuccessful.

All 17-CPO derivatives prepared showed (*E*)-configuration of the C=N double bond, as followed from the value of the chemical shift of protons H-18 (0.91–0.95 ppm). This range is typical for 17-oximino derivatives with this configuration[6]. The other isomer was not found in the reaction mixture in accord with the findings[3,7] on 17-CMO and 17-CEO derivatives.

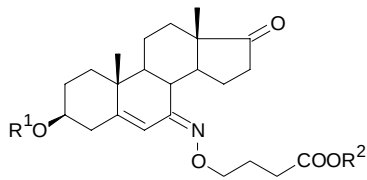
Recently, we presented the preparation of 7-CMO derivative of dehydroepiandrosterone[8] suitable for the immunoassay of this hormone (DHEA). For comparison we prepared by the analogical way 7-CPO DHEA **12**. The starting 7-keto derivative **9** was transformed by the reaction with *O*-(3-carboxypropyl)hydroxylamine in pyridine and subsequent methylation by diazomethane into methyl ester of 7-CPO derivative **10**. The steric reasons, as in the case of 7-CMO derivatives[8], gave rise to only (7*Z*)-isomer. By oxidation of 17-hydroxy group in **10** by Jones reagent the ketone **11** was prepared and subsequent alkaline hydrolysis of protecting groups gave 7-CPO derivative **12**. Its ^{1}H NMR spectrum displayed signals of $=NO(CH_2)_3COOH$ moiety: triplet of methylene next to NO at δ 4.10 (J = 6.1 Hz) and triplet of methylene neighboring with COOH at δ 2.48 (J = 7.4 Hz), further doublet H-6 at δ 6.47 (J = 1.5 Hz) and multiplet of H-3 at δ 3.64 (W = 32 Hz). The mass spectrum was also in accord with structure **12**: molecular ion *m/z* 403 was found besides the ion *m/z* 300, corresponding to the loss of the $O(CH_2)_3COOH$ fragment. The IR spectrum contained the bands at 3 412 cm^{-1} (O–H assoc.), 2 700 cm^{-1} (COOH assoc.), 1 735 cm^{-1} (C=O), 1 634 cm^{-1} (C=C) and 935 cm^{-1} (N–O).

The synthesis of 3-CPO derivative of testosterone was performed by several ways. In the first approach the testosterone (**14**) was reacted with *O*-(3-carboxypropyl)hydroxylamine in pyridine to give a mixture of oxime isomers in the ratio 1 : 1, *i.e.* 3-CPO derivatives **16** and **20**. The reaction with diazomethane yielded corresponding isomeric methyl esters **17** and **21**, which were separated by the column chromatography on silica

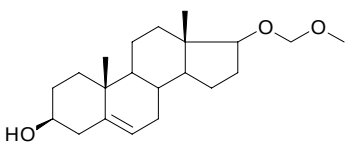
gel. By the hydrolysis, the free 3-CPO isomers **16** and **20** were prepared and could be fully differentiated by spectral methods. In the ^{1}H NMR spectrum of (3*E*)-CPO derivative **16** the doublet H-4 was found at δ 5.76 (*J* = 1.2 Hz), triplet =NOCH$_2$ at δ 4.09 (*J* = 6.1 Hz), triplet H-17α at δ 3.62 (*J* = 8.3 Hz), signal H-2α (ddd, *J*(1β,2α) = 2.8, *J*(1α,2α) = 4.6, *J*(2α,2β) = 17.4 Hz) at δ 2.94 and triplet CH$_2$COO at δ 2.41 (*J* = 7.3 Hz).



9, X = O
10, X = NO(CH$_2$)$_3$COOCH$_3$ (7*Z*)



	R^1	R^2
11	Ac	CH_3
12	H	H



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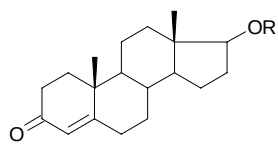
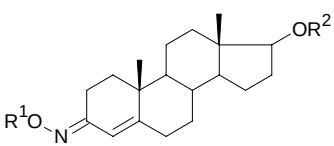
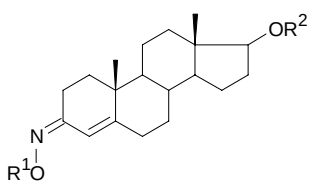


14, R = H
15, R = MOM



	R^1	R^2
16	$(CH_2)_3COOH$	H
17	$(CH_2)_3COOCH_3$	H
18	H	MOM
19	$(CH_2)_3COOCH_2CH_3$	MOM

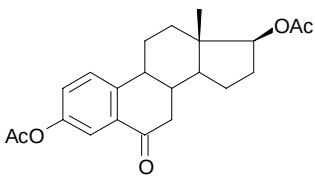


	R^1	R^2
20	$(CH_2)_3COOH$	H
21	$(CH_2)_3COOCH_3$	H
22	H	MOM
23	$(CH_2)_3COOCH_2CH_3$	MOM

In the spectrum of (3*Z*)-CPO derivative **20** the signal H-4 was shifted downfield to δ 6.36, whereas other signals were about of the same values as in (3*E*)-CPO derivative **16**, except for the H-2α signal overlapped by the steroid skeleton protons envelope. The assignment of the configuration on the C=N double bond was analogous to the corresponding 3-CMO and 3-CEO derivatives of testosterone[4,9].

The second approach was based on the MOM derivative of testosterone **15**, prepared from hydroxy derivative **13**. Its reaction with hydroxylamine in pyridine gave oxime as the mixture of (3*E*)- and (3*Z*)-isomers **18** and **22** in the 4 : 1 ratio. These isomers were separated by preparative chromatography. From both isomers **18** and **22** the respective sodium salts were prepared and their reactions with ethyl 4-bromobutyrate gave corresponding (3*E*)- and (3*Z*)-isomers of ethyl esters 3-CPO derivatives **19** and **23**. The cleavage of MOM protecting group in acidic medium in a methanol–benzene mixture was accompanied besides expected transesterification to methyl esters also by undesirable isomerization about the C=N bond. In both cases a mixture of (3*E*)- and (3*Z*)-isomers of methyl esters **17** and **21** was obtained in the 1 : 1 ratio.

The synthesis of 3-CPO derivatives of testosterone by sequential *O*-alkylation was found to be less efficient: the yields were generally low and when the MOM protection was used, the isomerization during the cleavage of protecting group was observed.



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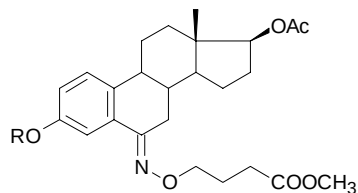
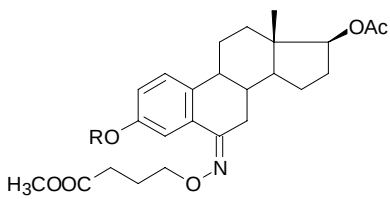


25, R = Ac
26, R = H



27, R = Ac
28, R = H

The last steroid skeleton under study was estrane. The 6-oxoestradiol diacetate (**24**) with *O*-(3-carboxypropyl)hydroxylamine in pyridine gave after subsequent diazomethane methylation a mixture of products, from which the methyl esters 6-CPO derivatives **25** and **27** were separated in about 10 : 1 ratio, besides products of hydrolysis of 3-acetate in the same ratio (**26** and **28**). The assignment of (6*E*)- and (6*Z*)-configuration was done from ^{1}H NMR spectra, in which the shifts of H-4 were quite different: for (6*E*)-isomer **25** the signal was found at δ 7.66, for (6*Z*)-isomer **27** was shifted downfield to δ 8.30. Even the difference in the shifts for H-7β was characteristic: in the case of (6*E*)-isomer the proximity of oxygen caused the deshielding and the signal was found at δ 3.06,

whereas for the (6*Z*)-isomer this proton resonates at δ 2.65. Common are triplets of methylene groups =NOCH_2 at δ *ca* 4.2 (*J* = 6.1 Hz) and CH_2COO at δ *ca* 2.4 (*J* = 7.3 Hz), 3- and 17-acetate protons, and protons H-1 and H-2 on the ring A. The structure was further confirmed by the IR and mass spectra. Again the fragmentation by the rupture of N–O bond in MS was observed and the ions originated from the loss of O$(CH_2)_3$COOR fragment were found. This behavior is analogical to the fragmentation of esters of steroid CMO or CEO derivatives[3,10].

EXPERIMENTAL

Melting points were determined on a Boetius micro melting point apparatus (Germany). Optical rotations were measured at 25 °C on a Perkin–Elmer 141 MC polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra (wavenumbers in cm^{-1}) were recorded on a Bruker IFS 88 spectrometer in chloroform unless stated otherwise. ^{1}H NMR spectra were taken on a Varian UNITY-200 (200 MHz, FT mode) at 23 °C in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) and width of multiplets (*W*) in Hz. Mass spectra were recorded on a VG Analytical ZAB-EQ spectrometer (energy of ionizing electrons 70 eV, ion source temperature 180–220 °C). Thin-layer chromatography was performed on silica gel G (ICN Biochemicals), with detection by spraying with concentrated sulfuric acid followed by heating. Preparative TLC was done on plates 200 × 200 mm, layer thickness 0.4 mm. For column chromatography silica gel 60–120 μm was used. Prior to evaporation on rotary evaporator *in vacuo* (bath temperature 50 °C), solutions in organic solvents were dried over anhydrous sodium sulfate. *O*-(3-Carboxypropyl)hydroxylamine hydrochloride was prepared according to the literature[11].

(17*E*)-17-Oxoandrost-5-en-3β-yl Acetate *O*-(3-Carboxypropyl)oxime (**4**)

O-(3-Carboxypropyl)hydroxylamine hydrochloride (1.16 g, 7.5 mmol) was added to a solution of dehydroepiandrosterone acetate (**1**, 1.65 g, 5.0 mmol) in pyridine (17 ml). After stirring at 60 °C for 6 h, the solvent was evaporated *in vacuo*, the residue was coevaporated with toluene (75 ml, three times) and partitioned between ether and water. Aqueous phase was extracted with ether and combined organic phases were washed successively with dilute hydrochloric acid (1 : 4) and water (three times). The solvent was evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (20 g) in a benzene–acetone mixture (98 : 2). Yield of CPO derivative **4** was 1.50 g (70%), m.p. 123–125 °C (light petroleum–ether), $[\alpha]_D$ –41° (*c* 1.1, chloroform). ^{1}H NMR spectrum: 5.39 d, 1 H, *J* = 5.8 (H-6); 4.61 m, 1 H, *W* = 31 (H-3α); 4.09 t, 2 H, *J* = 6.1 (NOCH_2); 2.47 t, 2 H, *J* = 7.3 (CH_2COO); 2.04 s, 3 H (CH_3COO); 1.05 s, 3 H (3 × H-19); 0.92 s, 3 H (3 × H-18). IR spectrum: 3 518 (O–H, carboxyl, monomer); 2 713 (O–H, carboxyl, assoc.); 1 740 (C=O, acetate); 1 713 (C=O, carboxyl, dimer); 1 670 (C=C); 1 650 (C=N); 1 254 (C–O). Mass spectrum, *m/z* (%): 371 (42, M – CH_3COOH), 328 (5, M – O$(CH_2)_3$COOH), 268 (100, M – CH_3COOH – O$(CH_2)_3$COOH), 211 (15), 96 (23), 43 (24). For $C_{25}H_{37}NO_5$ (431.6) calculated: 69.56% C, 8.66% H, 3.25% N; found: 69.77% C, 8.78% H, 3.24% N.

(17*E*)-3β-Hydroxyandrost-5-en-17-one *O*-(3-Carboxypropyl)oxime (**5**)

A) Acetate **4** (206 mg, 0.48 mmol) was dissolved in a mixture of tetrahydrofuran (4.5 ml) and methanol (0.75 ml). After addition of 0.4 M aqueous sodium hydroxide (3 ml), the mixture was stirred at 42 °C for 3 h. The excess alkali was neutralized with dilute hydrochloric acid (1 : 4) and

the solvents were evaporated *in vacuo*. The residue was extracted with ether (250 ml). The extract was washed with water and the solvent was evaporated *in vacuo*. The residue was crystallized from methanol–water, yielding 160 mg (86%) of compound **5**, m.p. 177-181 °C, $[\alpha]_D$ –38° (*c* 1.2, dioxane). ^{1}H NMR spectrum: 5.36 d, 1 H, *J* = 5.2 (H-6); 4.05 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.50 m, 1 H, *W* = 31 (H-3α); 2.40 t, 2 H, *J* = 7.3 (CH_2COO); 1.03 s, 3 H (3 × H-19); 0.92 s, 3 H (3 × H-18). IR spectrum (KBr pellet): 3 400 (O–H, carboxyl, assoc.); 1 687 (C=O, carboxyl); 1 046 (C–O); 949 (N–O). Mass spectrum, *m/z* (%): 389 (8, M^+), 286 (100, M – $O(CH_2)_3COOH$), 268 (31, M – $O(CH_2)_3COOH$ – H_2O), 211 (12), 159 (18), 105 (29). For $C_{23}H_{35}NO_4$ (389.5) calculated: 70.92% C, 9.06% H, 3.60% N; found: 71.08% C, 9.17% H, 3.51% N.

B) Ester **7** (110 mg, 0.27 mmol) was dissolved in 2 M methanolic sodium hydroxide solution (10 ml) and the reaction mixture was stirred at room temperature for 2.5 h. The mixture was acidified with dilute hydrochloric acid (1 : 4) and the product was extracted with ether. The extract was washed with dilute hydrochloric acid (1 : 4) and water and the solvent was evaporated *in vacuo*. Crystallization of the residue from a methanol–water mixture afforded 73 mg (69%) of compound **5**, m.p. 176–179 °C, $[\alpha]_D$ –38° (*c* 1.2, dioxane).

(17*E*)-3β-(Methoxymethoxy)androst-5-en-17-one *O*-(3-Carboxypropyl)oxime Ethyl Ester (**6**)

A solution of oxime[3] **3** (346 mg, 1.0 mmol) in dioxane (7 ml) was added under argon to a sodium hydride (96 mg, 4.0 mmol) and the reaction mixture was stirred under argon at 90 °C for 4 h. Then ethyl 4-bromobutyrate (0.58 ml, 4.0 mmol) was added and the stirring continued at the same temperature for 14 h. The mixture was acidified with dilute hydrochloric acid (1 : 4) and the product was extracted with ether (twice). Combined organic phases were washed successively with dilute hydrochloric acid (1 : 4), water, saturated aqueous potassium hydrogen carbonate solution and water. After drying the solvent was evaporated *in vacuo* and the residue was coevaporated with toluene (twice). Chromatography on a column of silica gel (10 g) in a benzene–ether mixture (98 : 2) afforded 280 mg (81%) of starting oxime **3** and 60 mg (13%) of oily ester **6**. ^{1}H NMR spectrum: 5.38 d, 1 H, *J* = 4.1 (H-6); 4.69 s, 2 H (OCH_2O); 4.13 q, 2 H, *J* = 7.3 ($COO\mathbf{CH}_2CH_3$); 4.03 t, 2 H, *J* = 6.4 ($NOCH_2$); 3.43 m, 1 H, *W* = 32 (H-3α); 3.69 s, 3 H (OCH_3); 2.39 t, 2 H, *J* = 7.3 (CH_2COO); 1.25 t, 3 H, *J* = 7.3 ($COOCH_2\mathbf{CH}_3$); 1.03 s, 3 H (3 × H-19); 0.91 s, 3 H (3 × H-18). IR spectrum: 1 728 (C=O); 1 660 (C=C); 1 653 (C=N); 1 146, 1 103, 1 038 (C–O–C); 940 (N–O). Mass spectrum, *m/z* (%): 461 (5, M^+), 417 (71), 400 (75), 330 (15, M – $O(CH_2)_3COOC_2H_5$), 268 (92), 115 (84), 45 (100). For $C_{27}H_{43}NO_5$ (461.6) calculated: 70.25% C, 9.39% H, 3.03% N; found: 70.48% C, 9.56% H, 2.82% N.

(17*E*)-3β-Hydroxyandrost-5-en-17-one *O*-(3-Carboxypropyl)oxime Methyl Ester (**7**)

A) Concentrated hydrochloric acid (200 μl) was added to a solution of compound **8** (367 mg, 0.85 mmol) in a methanol-benzene mixture (26 ml, 1 : 1). Reaction mixture was heated to 40 °C for 2 h and then allowed to stand at room temperature for 2 h. After evaporation of solvents *in vacuo*, the residue was dissolved in ether, the extract was washed with water and ether was evaporated *in vacuo*. Chromatography of the residue on a column of silica gel (15 g) in a benzene–ether mixture (96 : 4) followed by crystallization from light petroleum–ether mixture afforded 250 mg (73%) of compound **7**, m.p. 69–73 °C, $[\alpha]_D$ –42° (*c* 1.4, chloroform). ^{1}H NMR spectrum: 5.36 d, 1 H, *J* = 4.9 (H-6); 4.04 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.68 s, 3 H (OCH_3); 3.53 m, 1 H, *W* = 31 (H-3α); 2.41 t, 2 H, *J* = 7.3 (CH_2COO); 1.03 s, 3 H (3 × H-19); 0.91 s, 3 H (3 × H-18). IR spectrum: 3 609, 3 500 (O–H); 1 732 (C=O); 1 670 (C=C); 1 653 (C=N); 1 048 (C–O). Mass spectrum, *m/z* (%): 403 (8, M^+), 388 (8), 286 (100, M – $O(CH_2)_3COOCH_3$), 271 (30), 268 (61), 254 (10), 101 (77, $(CH_2)_3COOCH_3$). For $C_{24}H_{37}NO_4$ (403.6) calculated: 71.43% C, 9.24% H, 3.47% N; found: 71.16% C, 9.33% H, 3.40% N.

B) Concentrated hydrochloric acid (200 μl) was added to a solution of compound **6** (40 mg, 87 μmol) in a methanol–benzene mixture (4 ml, 1 : 1). Reaction mixture was heated to 40 °C for 6 h and then diluted with benzene (50 ml). The solvents were evaporated *in vacuo* and the residue was dissolved in ether and water. Aqueous phase was extracted with ether, the combined ethereal phases were washed successively with saturated aqueous potassium hydrogen carbonate solution and water. After drying the solvent was evaporated *in vacuo*. Chromatography of the residue on preparative silica gel plate in a benzene–ether mixture (6 : 4) gave 30 mg (85%) of compound **7**, m.p. 68–72 °C (ether–petroleum ether), $[\alpha]_D$ –42° (*c* 1.2, chloroform).

(17*E*)-3β-(Methoxymethoxy)androst-5-en-17-one *O*-(3-Carboxypropyl)oxime (**8**)

O-(3-Carboxypropyl)hydroxylamine hydrochloride (930 mg, 6.0 mmol) was added to a solution of ketone[12] **2** (996 mg, 3.0 mmol) in pyridine (10 ml). After stirring at 60 °C for 4 h, the reaction mixture was coevaporated with toluene (twice). The residue was partitioned between ether and water. Aqueous phase was extracted with ether and combined organic phases were washed with dilute hydrochloric acid (1 : 4) and water. After drying the solvent was evaporated *in vacuo* and the residue (1.23 g) was crystallized from a methanol–water mixture. Yield 970 mg (75%) of compound **8**, m.p. 119–122 °C, $[\alpha]_D$ –37° (*c* 1.3, chloroform). ^{1}H NMR spectrum: 5.36 d, 1 H, *J* = 4.3 (H-6); 4.69 s, 2 H (OCH_2O); 4.08 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.43 m, 1 H, *W* = 32 (H-3α); 3.37 s, 3 H (OCH_3); 2.46 t, 2 H, *J* = 7.3 (CH_2COO); 1.03 s, 3 H (3 × H-19); 0.92 s, 3 H (3 × H-18). IR spectrum: 1 709 (C=O, dimer COOH); 1 660 (C=C); 1 145, 1 102, 1 040 (O–C–O); 950 (N–O). Mass spectrum, *m/z* (%): 433 (26, M^+), 418 (21), 386 (60), 377 (73), 371 (82), 330 (16, M – $O(CH_2)_3COOH$), 268 (100). For $C_{25}H_{39}NO_5$ (433.6) calculated: 69.25% C, 9.07% H, 3.23% N; found: 69.34% C, 9.21% H, 3.25% N.

(7*Z*)-17β-Hydroxy-7-oxoandrost-5-en-3β-yl Acetate *O*-(3-Carboxypropyl)oxime Methyl Ester (**10**)

A mixture of ketone[8] **9** (370 mg, 1.1 mmol), *O*-(3-carboxypropyl)hydroxylamine hydrochloride (332 mg, 2.1 mmol), and pyridine (3.5 ml) was heated under stirring to 60 °C for 4.5 h. Toluene (20 ml) was added and the solvents were evaporated *in vacuo*. The residue was dissolved in ether (150 ml) and water, the aqueous phase was extracted with ether, combined organic phases were washed with dilute hydrochloric acid (1 : 4) and water, and the solvent was evaporated *in vacuo*. The residue was dissolved in ether (20 ml) and methanol (5 ml) and treated with ethereal solution of diazomethane at 0 °C for 5 min. The excess diazomethane and the solvents were evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (20 g) in a benzene–ethyl acetate mixture (93 : 7). Crude product was crystallized from a methanol–water mixture. Yield of compound **10** was 350 mg (69%), m.p. 71–74 °C, $[\alpha]_D$ –194° (*c* 1.1, chloroform). ^{1}H NMR spectrum: 6.45 d, 1 H, *J* = 1.5 (H-6); 4.64 m, 1 H, *W* = 32 (H-3α); 4.05 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.68 s, 3 H ($COOCH_3$); 3.67 m, *W* = 18.3 (H-17α); 2.41 t, 2 H, *J* = 7.3 (CH_2COO); 2.04 s, 3 H (CH_3COO); 1.13 s, 3 H (3 × H-19); 0.77 s, 3 H (3 × H-18). IR spectrum: 3 613 (O–H); 1 728 (C=O); 1 638 (C=C); 1 250 (C–O); 1 033 (C–O); 927 (N–O). Mass spectrum, *m/z* (%): 462 (21, M + H^+), 446 (16), 401 (57, M – CH_3COOH), 371 (18), 284 (27, M – CH_3COOH – $O(CH_2)_3COOCH_3$), 101 (100). For $C_{26}H_{39}NO_6$ (461.6) calculated: 67.65% C, 8.52% H, 3.03% N; found: 67.70% C, 8.59% H, 2.98% N.

(7*Z*)-7,17-Dioxoandrost-5-en-3β-yl Acetate 7-[*O*-(3-Carboxypropyl)oxime] Methyl Ester (**11**)

Jones reagent (0.3 ml) was added to a solution of hydroxy derivative **10** (230 mg, 0.5 mmol) in acetone (20 ml). After stirring at room temperature for 10 min, the excess reagent was decomposed by methanol (4 ml). The solvents were evaporated *in vacuo*, the residue was partitioned between ether and water. Aqueous phase was extracted with ether, the combined ethereal phases were washed

with water, saturated aqueous potassium hydrogen carbonate solution and water. The solvent was evaporated and the residue was crystallized from a light petroleum–ether mixture. Yield of ketone **11** was 225 mg (98%), m.p. 92–95 °C, $[\alpha]_D$ –155° (*c* 1.1, chloroform). ^{1}H NMR spectrum: 6.49 d, 1 H, *J* = 1.5 (H-6); 4.65 m, 1 H, *W* = 32 (H-3α); 4.08 t, 2 H, *J* = 6.0 ($NOCH_2$); 3.68 s, 3 H ($COOCH_3$); 2.42 t, 2 H, *J* = 7.3 (CH_2COO); 2.04 s, 3 H (CH_3COO); 1.14 s, 3 H (3 × H-19); 0.91 s, 3 H (3 × H-18). IR spectrum: 1 731 (C=O); 1 638 (C=C); 1 250 (C–O); 926 (N–O). Mass spectrum, *m/z* (%): 460 (18, M + H^+), 429 (29), 399 (58), 369 (13), 282 (16, M – CH_3COOH – $O(CH_2)_3COOCH_3$), 254 (34), 239 (19), 101 (100). For $C_{26}H_{37}NO_6$ (459.6) calculated: 67.95% C, 8.11% H, 3.05% N; found: 67.71% C, 8.17% H, 2.93% N.

(7*Z*)-3β-Hydroxyandrost-5-ene-7,17-dione 7-[*O*-(3-Carboxypropyl)oxime] (**12**)

Compound **11** (200 mg, 0.44 mmol) was dissolved in a tetrahydrofuran (4.5 ml) and methanol (0.75 ml) mixture. After addition of 0.4 M aqueous sodium hydroxide (2.9 ml) the mixture was stirred at 42 °C for 3 h. The excess alkali was neutralized with dilute hydrochloric acid (1 : 4) and the solvents were evaporated *in vacuo*. The residue was acidified with dilute hydrochloric acid (1 : 4) and the product was extracted with ether (250 ml). The extract was washed with water (three times) and the solvent was evaporated *in vacuo*. Chromatography of the residue on a column of silica gel (20 g) in a chloroform–methanol mixture (99 : 1) afforded 130 mg (79%) of compound **12**, m.p. 198–214 °C (decomp., methanol–water), $[\alpha]_D$ –150° (*c* 1.1, dioxane). ^{1}H NMR spectrum: 6.47 d, 1 H, *J* = 1.5 (H-6); 4.10 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.64 m, 1 H, *W* = 32 (H-3α); 2.48 t, 2 H, *J* = 7.4 (CH_2COO); 1.13 s, 3 H (3 × H-19); 0.91 s, 3 H (3 × H-18). IR spectrum: 3 412 (O–H); 2 700 (O–H, carboxyl, assoc.); 1 735 (C=O, ketone); 1 711 (C=O, carboxyl); 1 634 (C=C); 935 (N–O). Mass spectrum, *m/z* (%): 403 (15, M^+), 375 (11), 347 (10), 300 (13, M – $O(CH_2)_3COOH$), 273 (100), 258 (84), 255 (39), 240 (55), 204 (16), 191 (48), 178 (44), 160 (76). For $C_{23}H_{33}NO_5$ (403.5) calculated: 68.46% C, 8.24% H, 3.47% N; found: 68.47% C, 8.28% H, 3.41% N.

Reaction of Testosterone (**14**) with *O*-(3-Carboxypropyl)hydroxylamine

A mixture of testosterone (**14**, 2.88 g, 10 mmol), *O*-(3-carboxypropyl)hydroxylamine hydrochloride (3.10 g, 20 mmol), and pyridine (35 ml) was heated under stirring to 60 °C for 2.5 h. Toluene (50 ml) was added and the solvents were evaporated *in vacuo*. The residue was dissolved in ether and water, the aqueous phase was extracted with ether, combined organic phases were washed with dilute hydrochloric acid (1 : 4) and water, and the solvent was evaporated *in vacuo*. Yield of a mixture of isomeric 3-CPO derivatives **16** and **20** was 3.86 g (99%).

This mixture was dissolved in ether (150 ml) and methanol (20 ml) and treated with ethereal solution of diazomethane at 0 °C for 5 min. The excess diazomethane and the solvents were evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (370 g) in a light petroleum–benzene–ethyl acetate mixture (50 : 45 : 5) to give following compounds:

*(3E)-17*β*-Hydroxyandrost-4-en-3-one O-(3-carboxypropyl)oxime methyl ester* (**17**), yield 2.03 g (51%), m.p. 103–105 °C (ether), $[\alpha]_D$ +126° (*c* 1.1, chloroform). ^{1}H NMR spectrum: 5.75 d, 1 H, *J* = 1.2 (H-4); 4.07 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.67 s, 3 H (OCH_3); 3.62 t, 1 H, *J* = 8.2 (H-17α); 2.94 ddd, 1 H, *J*(1β,2α) = 2.8, *J*(1α,2α) = 4.6, *J*(2α,2β) = 17.4 (H-2α); 2.41 t, 2 H, *J* = 7.3 (CH_2COO); 1.06 s, 3 H (3 × H-19); 0.77 s, 3 H (3 × H-18). IR spectrum: 3 614 (O–H); 1 737 (C=O); 1 632 (C=N); 1 236, 1 053 (C–O). Mass spectrum, *m/z* (%): 403 (32, M^+), 373 (12), 358 (8), 314 (21), 286 (11, M – $O(CH_2)_3COOCH_3$), 123 (32), 101 (100). For $C_{24}H_{37}NO_4$ (403.6) calculated: 71.42% C, 9.26% H, 3.47% N; found: 71.50% C, 9.49% H, 3.42% N.

*(3Z)-17*β*-Hydroxyandrost-4-en-3-one O-(3-carboxypropyl)oxime methyl ester* (**21**), yield 1.86 g (47%), m.p. 117–120 °C (ether), $[\alpha]_D$ +187° (*c* 1.2, chloroform). ^{1}H NMR spectrum: 6.36 d, 1 H, *J* =

1.5 (H-4); 4.06 t, 2 H, J = 6.1 ($NOCH_2$); 3.67 s, 3 H (OCH_3); 3.63 t, 1 H, J = 8.2 (H-17α); 2.43 t, 2 H, J = 7.3 (CH_2COO); 1.10 s, 3 H (3 × H-19); 0.77 s, 3 H (3 × H-18). IR spectrum: 3 614 (O–H); 1 732 (C=O); 1 625 (C=N); 1 244, 1 054 (C–O). Mass spectrum, *m/z* (%): 403 (38, M^+), 373 (15), 358 (11), 314 (27), 286 (14, M – $O(CH_2)_3COOCH_3$), 123 (37), 101 (100). For $C_{24}H_{37}NO_4$ (403.6) calculated: 71.42% C, 9.26% H, 3.47% N; found: 71.21% C, 9.46% H, 3.42% N.

(3*E*)-17β-Hydroxyandrost-4-en-3-one *O*-(3-Carboxypropyl)oxime (**16**)

Methyl ester **17** (250 mg, 0.62 mmol) was dissolved in 2 M methanolic sodium hydroxide (25 ml) and the mixture was stirred at room temperature for 1 h. Reaction mixture was acidified with dilute hydrochloric acid (1 : 4) and the product was extracted with ethyl acetate (200 ml). The extract was washed with water (four times) and the solvent was evaporated *in vacuo*. Crystallization from ether afforded 220 mg (91%) of acid **16**, m.p. 189–193 °C, $[\alpha]_D$ +117° (*c* 1.2, dioxane). ^{1}H NMR spectrum: 5.76 d, 1 H, J = 1.2 (H-4); 4.09 t, 2 H, J = 6.1 ($NOCH_2$); 3.62 t, 1 H, J = 8.3 (H-17α); 2.94 ddd, 1 H, J(1β,2α) = 2.8, J(1α,2α) = 4.6, J(2α,2β) = 17.4 (H-2α); 2.41 t, 2 H, J = 7.3 (CH_2COO); 1.06 s, 3 H (3 × H-19); 0.78 s, 3 H (3 × H-18). IR spectrum: 3 610 (O–H, carboxyl, monomer); 3 500 (O–H, carboxyl, assoc.); 1 734 (C=O, carboxyl, monomer); 1 710 (C=O, carboxyl, assoc.); 1 624 (C=C); 928 (N–O). Mass spectrum, *m/z* (%): 389 (100, M^+), 374 (10), 359 (26), 344 (18), 314 (31), 286 (34, M – $O(CH_2)_3COOH$), 225 (24), 123 (66), 55 (37), 41 (36). For $C_{23}H_{35}NO_4$ (389.5) calculated: 70.92% C, 9.06% H, 3.60% N; found: 70.63% C, 9.06% H, 3.46% N.

(3*Z*)-17β-Hydroxyandrost-4-en-3-one *O*-(3-Carboxypropyl)oxime (**20**)

Methyl ester **21** (430 mg, 1.07 mmol) was dissolved in 2 M methanolic sodium hydroxide (43 ml) and the mixture was stirred for 1 h at room temperature. Reaction mixture was acidified with dilute hydrochloric acid (1 : 4) and the product was extracted with ethyl acetate (400 ml). The extract was washed with water (four times) and the solvent was evaporated *in vacuo*. Crystallization from a methanol–water mixture afforded 400 mg (96%) of acid **20**, m.p. 167–169 °C, $[\alpha]_D$ +183° (*c* 1.1, chloroform). ^{1}H NMR spectrum: 6.36 d, 1 H, J = 1.2 (H-4); 4.09 t, 2 H, J = 6.1 ($NOCH_2$); 3.64 t, 1 H, J = 8.4 (H-17α); 2.48 t, 2 H, J = 7.3 (CH_2COO); 1.10 s, 3 H (3 × H-19); 0.76 s, 3 H (3 × H-18). IR spectrum: 3 610 (O–H, carboxyl, monomer); 3 500 (O–H, carboxyl, assoc.); 1 735 (C=O, carboxyl, monomer); 1 710 (C=O, carboxyl, assoc.); 1 624 (C=C); 928 (N–O). Mass spectrum, *m/z* (%): 389 (100, M^+), 359 (29), 344 (20), 314 (37), 287 (48, M + H^+ – $O(CH_2)_3COOH$), 225 (27), 123 (86), 55 (82), 41 (89). For $C_{23}H_{35}NO_4$ (389.5) calculated: 70.92% C, 9.06% H, 3.60% N; found: 70.68% C, 9.14% H, 3.47% N.

17β-(Methoxymethoxy)androst-4-en-3-one (**15**)

1-Methylpiperidin-4-one (6.7 ml, 55 mmol) was added under argon to a solution of hydroxy derivative[13] **13** (3.40 g, 10.2 mmol) in toluene (135 ml). Some part (24 ml) of toluene was distilled off and 1 M solution of aluminum isopropoxide in toluene (8.7 ml) was added. After refluxing under argon for 6 h, the mixture was cooled, diluted with ether (250 ml) and washed successively with dilute hydrochloric acid (1 : 4), water, aqueous saturated potassium hydrogen carbonate solution, and water. The solvents were evaporated *in vacuo* and the residue was crystallized from methanol affording 3.2 g (94%) of ketone **15**, m.p. 123–124 °C (methanol), $[\alpha]_D$ +97° (*c* 1.3, chloroform), literature[14] gives m.p. 125–126 °C, $[\alpha]_D$ +109° (*c* 0.2, chloroform). ^{1}H NMR spectrum: 5.73 d, 1 H, J = 1.5 (H-4); 4.62 and 4.64, AB system, J(AB) = 6.4 (OCH_2O); 3.53 t, 1 H, J = 8.3 (H-17α); 3.35 s, 3 H (OCH_3); 1.19 s, 3 H (3 × H-19); 0.82 s, 3 H (3 × H-18). IR spectrum: 1 663 (C=O); 1 615 (C=C);

1 148, 1 102, 1 045 (O–C–O). Mass spectrum, *m/z* (%): 332 (22, M^+), 300 (29), 287 (18), 270 (6), 45 (100).

Reaction of Ketone **15** with Hydroxylamine

Hydroxylamine hydrochloride (0.83 g, 12.0 mmol) was added to a solution of ketone **15** (1.99 g, 6.0 mmol) in pyridine (20 ml). After stirring at 60 °C for 4 h, the mixture was coevaporated with toluene *in vacuo* (three times). The residue was partitioned between ether and water. Aqueous phase was extracted with ether and combined organic phases were washed successively with dilute hydrochloric acid (1 : 4), water, saturated aqueous potassium hydrogen carbonate and water. The solvent was evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (70 g) in a benzene–ether mixture (98 : 2) to give oxime isomers:

*(3E)-17*β*-(Methoxymethoxy)androst-4-en-3-one oxime* (**18**), yield 1.58 g (76%), m.p. 133–135 °C (methanol–water), $[\alpha]_D$ +108° (*c* 1.0, chloroform). ^{1}H NMR spectrum: 5.76 d, 1 H, *J* = 1.5 (H-4); 4.62 and 4.64, AB system, *J*(AB) = 6.7 (OCH_2O); 3.53 t, 1 H, *J* = 8.4 (H-17α); 3.35 s, 3 H (OCH_3); 3.04 ddd, 1 H, *J*(1β,2α) = 2.5, *J*(1α,2α) = 4.3, *J*(2α,2β) = 17.4 (H-2α); 1.07 s, 3 H (3 × H-19); 0.81 s, 3 H (3 × H-18). IR spectrum: 3 587, 3 272, 3 205 (O–H); 1 635 (C=N); 1 149, 1 102, 1 050 (C–O–C–O–C); 967, 939 (N–O). Mass spectrum, *m/z* (%): 347 (100, M^+), 332 (18), 302 (8), 286 (10), 268 (10), 139 (17), 45 (82). For $C_{21}H_{33}NO_3$ (347.5) calculated: 72.58% C, 9.57% H, 4.03% N; found: 72.74% C, 9.62% H, 3.97% N.

*(3Z)-17*β*-(Methoxymethoxy)androst-4-en-3-one oxime* (**22**), yield 360 mg (17%), m.p. 141–144 °C (light petroleum–ether). ^{1}H NMR spectrum: 6.47 d, 1 H, *J* = 0.9 (H-4); 4.62 and 4.64, AB system, *J*(AB) = 6.7 (OCH_2O); 3.52 t, 1 H, *J* = 8.4 (H-17α); 3.35 s, 3 H (OCH_3); 1.11 s, 3 H (3 × H-19); 0.81 s, 3 H (3 × H-18). IR spectrum: 3 590, 3 270, 3 205 (O–H); 1 631 (C=N); 1 149, 1 100, 1 050 (C–O–C–O–C); 968, 938, 908 (N–O). Mass spectrum, *m/z* (%): 347 (40, M^+), 332 (11), 302 (4), 298 (4), 285 (5), 268 (10), 139 (17), 45 (100). For $C_{21}H_{33}NO_3$ (347.5) calculated: 72.58% C, 9.57% H, 4.03% N; found: 72.80% C, 9.71% H, 3.95% N.

(3*E*)-17β-(Methoxymethoxy)androst-4-en-3-one *O*-(3-Carboxypropyl)oxime Ethyl Ester (**19**)

A solution of oxime **18** (347 mg, 1.0 mmol) in toluene (7 ml) was added under argon to sodium hydride (48 mg, 2.0 mmol) and the reaction mixture was stirred under argon at 90 °C for 3 h. Then ethyl 4-bromobutyrate (0.58 ml, 4.0 mmol) was added and stirring continued at the same temperature for 15 h. The mixture was acidified with dilute hydrochloric acid (1 : 4) and the product was extracted with ether (twice). Combined organic phases were washed successively with dilute hydrochloric acid (1 : 4), water, saturated aqueous potassium hydrogen carbonate solution and water. The solvent was evaporated *in vacuo* and the residue was coevaporated with toluene (twice). Chromatography on a column of silica gel (20 g) in a light petroleum–benzene–ether mixture (49 : 49 : 2) afforded 180 mg (39%) of oily ethyl ester **19**. ^{1}H NMR spectrum: 5.75 d, 1 H, *J* = 1.5 (H-4); 4.62 and 4.64, AB system, *J*(AB) = 6.7 (OCH_2O); 4.13 q, 2 H, *J* = 7.3 ($COO\mathbf{CH_2}CH_3$); 4.07 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.52 t, 1 H, *J* = 8.4 (H-17α); 3.35 s, 3 H (OCH_3); 2.95 ddd, 1 H, *J*(1β,2α) = 2.8, *J*(1α,2α) = 4.6, *J*(2α,2β) = 17.1 (H-2α); 2.41 t, 2 H, J = 7.3 (CH_2COO); 1.26 t, 3 H, *J* = 7.3 ($COOCH_2\mathbf{CH_3}$); 1.05 s, 3 H (3 × H-19); 0.81 s, 3 H (3 × H-18). IR spectrum: 1 728 (C=O); 1 632 (C=N); 1 149, 1 101, 1 050 (C–O–C–O–C); 968, 939 (N–O). Mass spectrum, *m/z* (%): 461 (20, M^+), 431 (10), 416 (10), 400 (2), 358 (15), 331 (6), 286 (5), 268 (3), 115 (84, $(CH_2)_3COOC_2H_5$), 45 (100). For $C_{27}H_{43}NO_5$ (461.6) calculated: 70.25% C, 9.39% H, 3.03% N; found: 70.55% C, 9.57% H, 2.96% N.

(3*Z*)-17β-(Methoxymethoxy)androst-4-en-3-one *O*-(3-Carboxypropyl)oxime Ethyl Ester (**23**)

A solution of oxime **22** (100 mg, 0.29 mmol) in toluene (5 ml) was added under argon to sodium hydride (24 mg, 1.0 mmol) and the reaction mixture was stirred under argon at 90 °C for 3 h. Then ethyl 4-bromobutyrate (0.25 ml, 1.7 mmol) was added and stirring continued at the same temperature for 15 h. The mixture was acidified with dilute hydrochloric acid (1 : 4) and the product was extracted with ether (twice). Combined organic phases were washed successively with dilute hydrochloric acid (1 : 4), water, saturated aqueous potassium hydrogen carbonate solution and water. The solvent was evaporated *in vacuo* and the residue was coevaporated with toluene (twice). Chromatography on a column of silica gel (10 g) in a benzene–ether mixture (99 : 1) afforded crude product which was purified by preparative thin-layer chromatography on two silica gel plates. Yield of oily ethyl ester **23** was 60 mg (45%). ^{1}H NMR spectrum: 6.37 d, 1 H, J = 1.5 (H-4); 4.62 and 4.64, AB system, J(AB) = 6.7 (OCH_2O); 4.13 q, 2 H, J = 7.3 ($COO\mathbf{CH_2}CH_3$); 4.06 t, 2 H, J = 6.1 ($NOCH_2$); 3.53 t, 1 H, J = 8.4 (H-17α); 3.35 s, 3 H (OCH_3); 2.42 t, 2 H, J = 7.3 (CH_2COO); 1.26 t, 3 H, J = 7.3 ($COOCH_2\mathbf{CH_3}$); 1.10 s, 3 H (3 × H-19); 0.81 s, 3 H (3 × H-18). IR spectrum: 1 728 (C=O); 1 626 (C=N); 1 149, 1 102, 1 050 (C–O–C–O–C); 968, 938 (N–O). Mass spectrum, *m/z* (%): 461 (27, M^+), 431 (14), 358 (20), 331 (20), 123 (38), 115 (98, $(CH_2)_3COOC_2H_5$), 87 (34), 45 (100). For $C_{27}H_{43}NO_5$ (461.6) calculated: 70.25% C, 9.39% H, 3.03% N; found: 70.48% C, 9.15% H, 2.97% N.

Cleavage of Methoxymethyl Protecting Group of Compound **19**

Concentrated hydrochloric acid (0.1 ml) was added to a solution of methoxymethoxy derivative **19** (35 mg, 76 μmol) in benzene (1.2 ml) and methanol (1.2 ml). After stirring at 42 °C for 9 h the solvents were evaporated *in vacuo*. The residue was partitioned between ether and water, aqueous phase was extracted with ether, the combined ethereal phases were washed with saturated aqueous potassium hydrogen carbonate solution and water. The solvent was evaporated and the residue was chromatographed on a preparative silica gel plate in a benzene–ether mixture (6 : 4) to give two products:

*(3E)-17*β*-Hydroxyandrost-4-en-3-one O-(3-carboxypropyl)oxime methyl ester* (**17**), yield 15 mg (49%), m.p. 103–105 °C (ether), $[\alpha]_D$ +126° (*c* 1.1, chloroform). The product was identical with the compound prepared by oximation of testosterone (see above).

*(3Z)-17*β*-Hydroxyandrost-4-en-3-one O-(3-carboxypropyl)oxime methyl ester* (**21**), yield 12 mg (39%), m.p. 117–120 °C (ether), $[\alpha]_D$ +187° (*c* 1.2, chloroform). The product was identical with the compound prepared by oximation of testosterone (see above).

Cleavage of Methoxymethyl Protecting Group of Compound **23**

Concentrated hydrochloric acid (0.4 ml) was added to a solution of methoxymethoxy derivative **23** (40 mg, 87 μmol) in benzene (2 ml) and methanol (2 ml). After stirring at 40 °C for 6 h the solvents were evaporated *in vacuo*. The residue was partitioned between ether and water, aqueous phase was extracted with ether, the combined ethereal phases were washed with saturated aqueous potassium hydrogen carbonate solution and water. The solvent was evaporated and the residue was chromatographed on one preparative silica gel plate in benzene–ether mixture (6 : 4) to give following compounds:

*(3E)-17*β*-Hydroxyandrost-4-en-3-one O-(3-carboxypropyl)oxime methyl ester* (**17**), yield 18 mg (51%), m.p. 103–106 °C (ether), $[\alpha]_D$ +126° (*c* 1.2, chloroform). The product was identical with the compound prepared by oximation of testosterone (see above).

*(3Z)-17*β*-Hydroxyandrost-4-en-3-one O-(3-carboxypropyl)oxime methyl ester* (**21**), yield 16 mg (46%), m.p. 118–120 °C (ether), $[\alpha]_D$ +186° (*c* 1.2, chloroform). The product was identical with the compound prepared by oximation of testosterone (see above).

Reaction of Ketone **24** with *O*-(3-Carboxypropyl)hydroxylamine

O-(3-Carboxypropyl)hydroxylamine hydrochloride (430 mg, 2.8 mmol) was added to a solution of ketone **24** (507 mg, 1.37 mmol) in pyridine (7 ml). After stirring at 52 °C for 6 h, another part of *O*-(3-carboxypropyl)hydroxylamine hydrochloride (230 mg, 1.5 mmol) was added and the stirring continued at the same temperature for 2 h. After cooling the reaction mixture was diluted with toluene (20 ml), the solvents were evaporated *in vacuo*, and the rest was coevaporated with toluene (20 ml). After dissolution in ether and water, the aqueous phase was extracted with ether, and combined organic phases were washed successively with dilute hydrochloric acid (1 : 4) and water (three times). The solvent was evaporated *in vacuo*, the residue was dissolved in ether (20 ml) and methanol (10 ml) and treated with ethereal solution of diazomethane at 0 °C for 10 min. The excess diazomethane and the solvents were evaporated *in vacuo* and the residue (640 mg) was chromatographed on a column of silica gel (65 g) in a benzene–ether mixture (97 : 3). The following compounds were separated according to increasing polarity:

*(6E)-6-Oxoestra-1,3,5(10)-triene-3,17*β*-diyl diacetate O-(3-carboxypropyl)oxime methyl ester* (**25**), yield 250 mg (38%) m.p. 117-118 °C (ether), $[\alpha]_D$ –24° (*c* 1.1, chloroform). ^{1}H NMR spectrum: 7.66 d, 1 H, *J*(2,4) = 2.4 (H-4); 7.31 d, 1 H, *J*(1,2) = 8.8 (H-1); 7.03 dd, 1 H, *J*(2,4) = 2.7, *J*(1,2) = 8.6 (H-2); 4.69 dd, 1 H, *J* = 7.6, *J*′= 9.2 (H-17α); 4.20 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.68 s, 3 H (OCH_3); 3.06 dd, 1 H, *J*(7β,8β) = 4.6, *J*(7α,7β) = 18.0 (H-7β); 2.44 t, 2 H, *J* = 7.3 (CH_2COO); 2.30 s, 3 H (CH_3COO); 2.07 s, 3 H (CH_3COO); 0.80 s, 3 H (3 × H-18). IR spectrum: 1 730 (C=O); 1 600 (C=N); 1 573 (C=C); 926 (N–O). Mass spectrum, *m/z* (%): 485 (29, M^+), 443 (29), 368 (11, M – $O(CH_2)_3COOCH_3$), 327 (100), 266 (15), 226 (10), 172 (23), 129 (12), 101 (92), 43 (21). For $C_{27}H_{35}NO_7$ (485.6) calculated: 66.79% C, 7.27% H, 2.88% N; found: 66.77% C, 7.37% H, 2.78% N.

*(6Z)-6-Oxoestra-1,3,5(10)-triene-3,17*β*-diyl diacetate O-(3-carboxypropyl)oxime methyl ester* (**27**), purification of crude product on preparative silica gel plate in a benzene–ether mixture (8 : 2), yield 26 mg (4%), m.p. 89–92 °C (chloroform). ^{1}H NMR spectrum: 8.30 d, 1 H, *J*(2,4) = 2.4 (H-4); 7.39 d, 1 H, *J*(1,2) = 8.5 (H-1); 7.09 dd, 1 H, *J*(2,4) = 2.7, *J*(1,2) = 8.6 (H-2); 4.70 dd, 1 H, *J* = 7.6, *J*′= 9.2 (H-17α); 4.16 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.66 s, 3 H (OCH_3); 2.65 dd, 1 H, *J*(7β,8β) = 4.0, *J*(7α,7β) = 14.6 (H-7β); 2.45 t, 2 H, *J* = 7.3 (CH_2COO); 2.32 s, 3 H (CH_3COO); 2.06 s, 3 H (CH_3COO); 0.83 s, 3 H (3 × H-18). IR spectrum: 1 730 (C=O); 1 607 (C=N); 1 576 (C=C); 932 (N–O). Mass spectrum, *m/z* (%): 485 (19, M^+), 443 (20), 369 (8, M + H^+ – $O(CH_2)_3COOCH_3$), 327 (82), 284 (11), 256 (8), 172 (16), 148 (18), 101 (100), 43 (24). For $C_{27}H_{35}NO_7$ (485.6) calculated: 66.79% C, 7.27% H, 2.88% N; found: 67.04% C, 7.43% H, 2.77% N.

*(6E)-3-Hydroxy-6-oxoestra-1,3,5(10)-trien-17*β*-yl acetate O-(3-carboxypropyl)oxime methyl ester* (**26**), yield 290 mg (48%) of crude compound. ^{1}H NMR spectrum: 7.42 d, 1 H, *J*(2,4) = 2.4 (H-4); 7.19 d, 1 H, *J*(1,2) = 8.8 (H-1); 6.82 dd, 1 H, *J*(2,4) = 2.7, *J*(1,2) = 8.6 (H-2); 4.69 dd, 1 H, *J* = 7.6, *J*′= 9.2 (H-17α); 4.20 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.68 s, 3 H (OCH_3); 3.06 dd, 1 H, *J*(7β,8β) = 4.6, *J*(7α,7β) = 18.0 (H-7β); 2.44 t, 2 H, *J* = 7.3 (CH_2COO); 2.07 s, 3 H (CH_3COO); 0.80 s, 3 H (3 × H-18).

*(6Z)-3-Hydroxy-6-oxoestra-1,3,5(10)-trien-17*β*-yl acetate O-(3-carboxypropyl)oxime methyl ester* (**28**), yield 20 mg (3%) of crude compound. ^{1}H NMR spectrum: 8.20 d, 1 H, *J*(2,4) = 2.4 (H-4); 7.32 d, 1 H, *J*(1,2) = 8.5 (H-1); 6.90 dd, 1 H, *J*(2,4) = 2.7, *J*(1,2) = 8.6 (H-2); 4.70 dd, 1 H, *J* = 7.6, *J*′= 9.2 (H-17α); 4.19 t, 2 H, *J* = 6.1 ($NOCH_2$); 3.66 s, 3 H (OCH_3); 2.75 dd, 1 H, *J*(7β,8β) = 4.0, *J*(7α,7β) = 14.6 (H-7β); 2.50 t, 2 H, *J* = 7.3 (CH_2COO); 2.07 s, 3 H (CH_3COO); 0.82 s, 3 H (3 × H-18).

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