APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2002; **16**: 628–634
Materials, Nanomaterials and Synthesis AOC
Published online in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/aoc.356

Hydroformylation – amidocarbonylation of androstene and pregnene derivatives†

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Received 7 January 2002; Accepted 5 July 2002

Androstene and pregnene derivatives were functionalized by amides with rhodium or binary rhodium–cobalt catalysts. Whereas the Rh–PPh_3 catalyzed reaction results in the unsaturated amido-methylidene derivatives, the rapid hydrogenation of these compounds takes place in the presence of a basic PR_3 ligand. Using a binary rhodium–cobalt system, amidocarbonylation of the steroids occurs with high chemo- and regio-selectivity. Our experiments did not support literature reports claiming the essential role of a bimetallic cluster as the active catalyst. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: steroid; homogeneous catalysis; amidocarbonylation; rhodium; cobalt

INTRODUCTION

The synthesis of amino acid derivatives has been the subject of increasing interest in the last few years. Among other syntheses, amidocarbonylation, discovered originally by Wakamatsu *et al.* in 1971,[1] is recognized as a key reaction. This powerful method is a special case of carbonylation, where aldehydes are transformed directly to *N*-acyl-amino acids in the presence of amides and catalytic amounts of cobalt complexes.

Combining this step with hydroformylation of olefins,[2] or with isomerization of allylic alcohols to the corresponding aldehydes,[3] as well as with isomerization of oxiranes,[4] new domino reaction sequences were developed. Whereas amidocarbonylation of aldehydes is catalyzed only by the cobalt carbonyl complexes, homogeneous bimetallic catalysts have been used more successfully for tandem reactions.[5] Working with fluoro-styrenes, Ojima et al.[6] carried out hydroformylation–amidocarbonylation efficiently in a mixed cobalt–rhodium-containing catalyst system. Further applications of amidocarbonylation, e.g. the synthesis of heterocyclic compounds, were developed by Izawa.[7]

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†This paper is based on work presented at the XIVth FECHEM Conference on Organometallic Chemistry held at Gdansk, Poland, 2–7 September 2001.
Contract/grant sponsor: Hungarian National Science Foundation; Contract/grant number: T 020185; Contract/grant number: T 034328.

In the past few years Beller and co-workers have described the palladium-catalyzed amidocarbonylation of aldehydes,[8] providing significant advantages over the cobalt system. They presented not only the applicability of the palladium-catalyzed amidocarbonylation, but also reported about newly synthesized important non-natural amino acids and the first application of acetals instead of aldehydes in this reaction.[9] The same group recently published a comprehensive review surveying all the important developments in this area.[10]

In this paper we report on selectively performed hydroformylation–amidocarbonylation reactions yielding new steroidal derivatives containing an α-amino acid moiety, compounds that have scarcely been described in the literature.[11]

RESULTS AND DISCUSSION

Hydroformylation–amidocarbonylation of androstene and pregnene derivatives in Rh–PR_3 catalytic systems

Working with the Rh–PPh_3 catalyst, unsaturated amido-methylidene compounds (**I**) are the major products (Scheme 1, Table 1). Addition of Et_3N supresses the side reactions and the hydroformylation product (**V**) of the substrate becomes dominant.

In the presence of the more basic PBu_3 ligand, rapid hydrogenation of **I** occurs and amido-methylene derivatives (**II**) are formed, especially after longer reaction times, but

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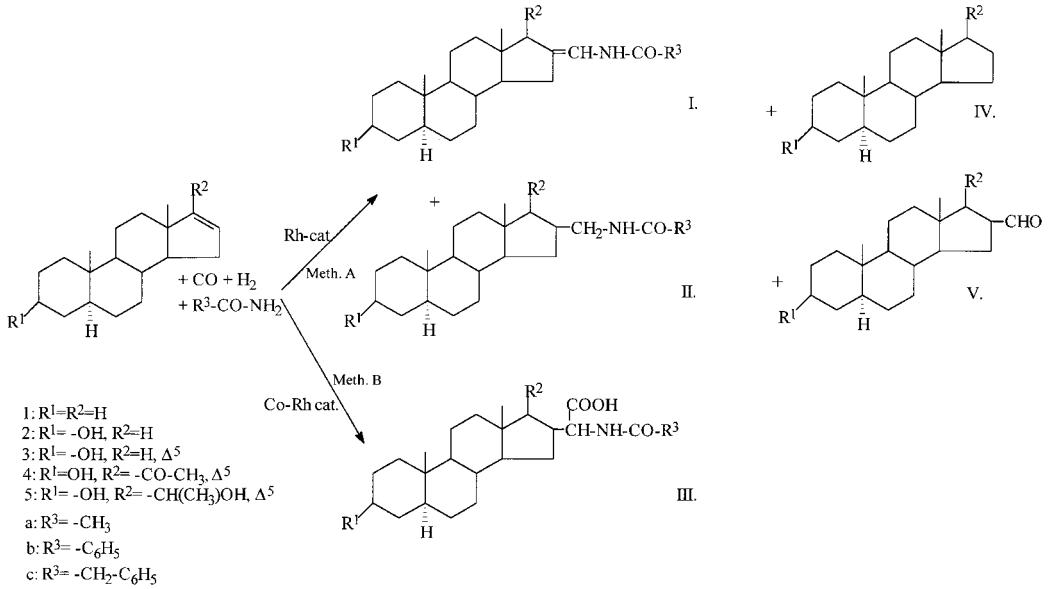

Scheme 1. Hydroformylation–amidocarbonylation of steroids.

this reaction is strongly influenced by the nature of the acylamino group. As we showed earlier,[12] formation of the aldehyde takes place in a highly regioselective reaction in the presence of a rhodium catalyst; consequently, the position of the functional groups derived consecutively from the formyl moiety is predetermined.

Hydroformylation–amidocarbonylation of androstene and pregnene derivatives in rhodium–cobalt bimetallic catalytic systems

Switching to the binary rhodium–cobalt catalyst system, *N*-acyl-α-amino acids (**III**) are the major products isolated in high yields in each case (Scheme 1, Table 2). Owing to the intermediacy of aldehyde, the reactions were run again in a highly chemo- and regio-selective manner. The high values determined are practically insensitive to the nature of the amide and the functionalization of the steroidal skeleton.

Gas-chromatographic analyses of the methylated product of 5α-androsta-16-ene showed that the substrate is converted rapidly into its 16-formyl derivative under the reaction conditions applied (Fig. 1). As consumed, this aldehyde is converted in parallel to enamide. Consecutively, the decrease in enamide concentration corresponds to an increase in amino acid. Confrontation of these data with the pathways suggested by Wakamatsu[2] led us to suppose the following steps in the hydroformylation–amidocarbonylation of unsaturated steroids (Scheme 2). In the first stage, the catalytically activated substrate is converted entirely to aldehyde, which forms a quite unstable addition product with the amide. Rapid water elimination results in enamide formation in a reversible step, followed by rhodium-

Table 1. Hydroformylation of steroids in the presence of amides with rhodium–phosphine catalysts[a]

Steroid	Amide	Phosphine	Reaction time (h)	Conversion (%)	Product distribution (%)			
					IV	**V**	**I**	**II**
1	CH_3CONH_2	PPh_3	48	99	11	34	55	0
1	CH_3CONH_2	$PPh_3 + Et_3N$	48	97	10	74	16	0
1	CH_3CONH_2	PBu_3	3	99	11	25	25	39
1	CH_3CONH_2	PBu_3	48	99	11	21	0	68
1	$C_6H_5CONH_2$	PPh_3	48	96	15	33	52	0
1	$C_6H_5CH_2CONH_2$	PPh_3	48	96	15	33	52	0
2	CH_3CONH_2	PPh_3	48	100	19	42	39	0
3	CH_3CONH_2	PPh_3	48	99	7	63	30	0

[a] Reaction conditions: 1.5 mmol steroid; 3 mmol amide; $p = 120$ bar H_2/CO (1:1); temperature, 120 °C. Solvent: dioxane; catalyst: 0.0375 mmol $\{[Rh(nbd)Cl]_2\}$ + 0.15 mmol phosphine.

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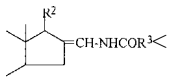
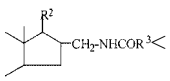
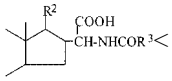
Table 2. Amidocarbonylation of steroids with a rhodium–cobalt binary system[a]

Steroid	Amide	Conversion[b] (%)	Product distribution[b] (%)			Isolated yield (%)
						
1	CH_3CONH_2	97	17	8	75	71
1	$C_6H_5CONH_2$	94	18	18	64	63
1	$C_6H_5CH_2CONH_2$	96	20	15	65	62
2	CH_3CONH_2	94	12	18	70	65
2	$C_6H_5CONH_2$	93	15	16	69	61
3	CH_3CONH_2	96	11	24	64	61
4	CH_3CONH_2	94	23	7	70	66
5	CH_3CONH_2	–[c]	–[c]	–[c]	–[c]	–[c]

[a] Reaction conditions: 1.5 mmol steroid; 3 mmol amide; p = 50 bar H_2 + 80 bar CO; temperature, 120 °C; time, 48 h. Solvent: dioxane; catalyst: 0.0375 mmol $\{[Rh(nbd)Cl]_2\}$ + 0.15 mmol PPh_3 + 0.0375 mmol $Co_2(CO)_8$.
[b] According to the GLC data of the methylated reaction mixture.
[c] Not detectable by GLC.

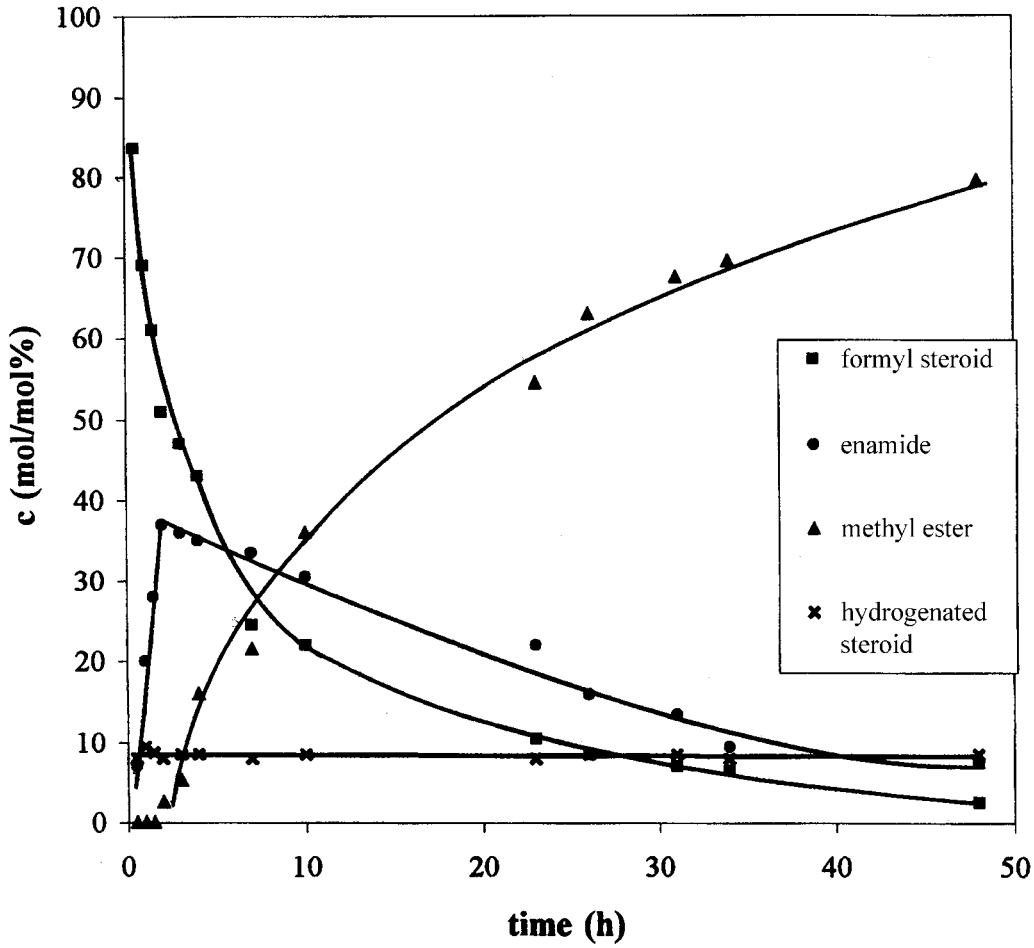


Figure 1. Hydroformylation–amidocarbonylation of androst-16-ene.

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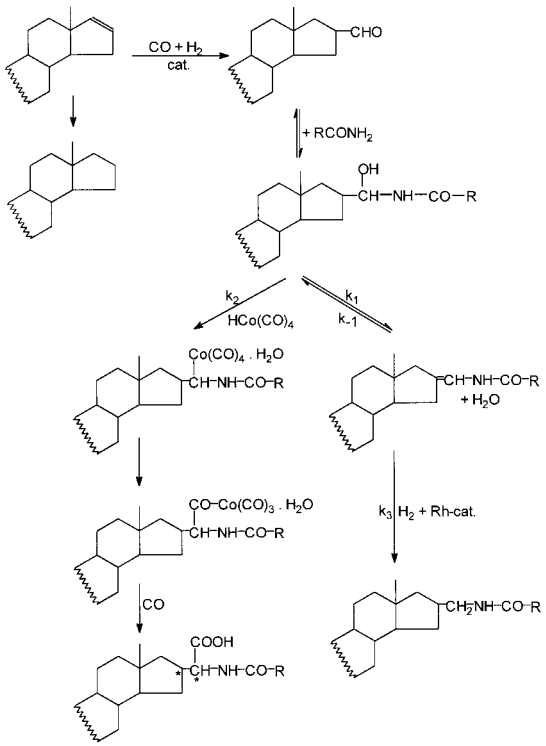
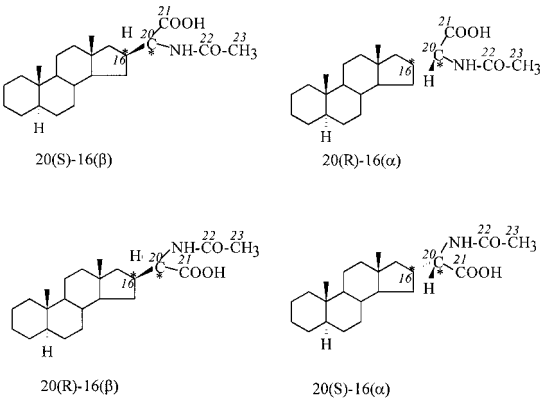


Scheme 2. Supposed pathways in hydroformylation–amidocarbonylation of androstene derivatives.

catalyzed hydrogenation of the C=C double bond. On the other hand, the intermediate product can react further with the active cobalt species, yielding the acid.

As far as the stereoselectivity of the reaction is concerned, four possible diastereomers should be taken into account: the α and β positions of the functional group on C-16 are associated with the *R* and *S* configurations of C-20 (Scheme 3). Determination of these stereoisomers was performed based on different NMR techniques (^{1}H, NOE, and ^{1}H–^{1}H COSY), so the multiplets given by the proton attached to



Scheme 3. Possible diastereomers formed in hydroformylation–amidocarbonylation of androst-16-ene.

Table 3. Dependence of the 16-α/16-β ratio on the phosphine ligand and the cobalt/rhodium ratio used in the reaction of **1**

Phosphine	Rh:P	Co/Rh	16-α/16-β
PPh_3	1:3.2	1	50/50
PPh_3	1:3.2	3	40/60
PPh_3	1:3.2	6	10/90
PBu_3	1:2.2	6	30/70
(+)-DIOP	1:3.2	1	45/55
(+)-DIOP	1:3.2	6	40/60
(+)-DIOP	1:3.2	10	45/55
CHIRAPHOS	1:3.2	6	50/50
2,2′-Dipyridyl	1:3.2	1	40/60
3,4,7,8-Tetramethylphenanthroline	1:3.2	1	40/60

C-20 could be assigned to the 16-α (downfield signal) and 16-β (upfield signal) positions. In the fine structure of these signals, a triplet and a doublet could be distinguished; each of these corresponds to the configurations of C-20.

This enabled us to determine the stereoselectivity of the process, which was studied by varying both the ligand and cobalt/rhodium ratio (Table 3). Although no significant effect could be observed when working with different achiral and chiral ligands, changing the cobalt/rhodium ratio resulted in an interesting increase in stereoselectivity up to $\alpha/\beta = 10/90$ at sixfold cobalt excess. To the best of our knowledge, this is the most successful example in stereoselective amidocarbonylation, since Parnaud *et al.* could not synthesize optically active amino acids starting from simple aldehydes.[13] The phenomenon observed by us should be attributed mainly to the asymmetric induction effect exerted by the steroidal skeleton as the only chiral element. Similar tendencies were also observed in other homogeneously catalyzed reactions.[14,15]

As far as the bimetallic catalyst system is concerned, there are some contradictory hypotheses in the literature regarding the active species formed. Studying the hydroformylation step, Horváth *et al.* detected a mixed cobalt–rhodium carbonyl cluster,[16] supposed later by Ojima *et al.* to be the active catalyst.[6] Later, based also on high-pressure IR spectroscopy, Garland[17] concluded from his experiments that the cluster formed under oxo conditions is rapidly decomposed and a rhodium acyl complex is generated. So, according to him, the "synergism" observed in the reaction arises exclusively from this facile fragmentation and not from cluster catalysis.[17]

Admitting these suppositions, our other goal was to gain some information regarding the catalytic aspects of the second, amidocarbonylation step in this one-pot reaction. For this purpose we chose vinyl-estrone as a model substrate, which was previously hydroformylated by Kollár *et al.* with high regio- and stereo-selectivity.[14]

Hydroformylation–amidocarbonylation of this substrate

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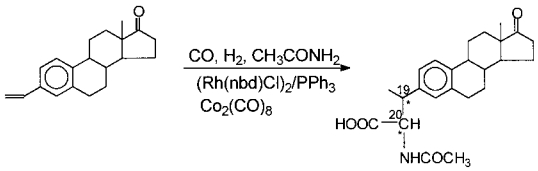

Scheme 4. Hydroformylation–amidocarbonylation of vinyl-estrone.

in the mixed rhodium–cobalt catalytic system led to the selective formation of the corresponding amino acid derivative possessing two new stereogenic centers (Scheme 4). The ^{1}H NMR spectrum of the isolated product enabled us to determine the diastereomeric ratios at both of these; we found that C-19 was racemized, and the ratio of the C-20 diastereomers was 1:4. Starting then from the pure aldehyde prepared according to the literature,[14] it was reacted with acetamide under the same conditions as before, but in the exclusive presence of $Co_2(CO)_8$. In this case the isolated product was analyzed again by ^{1}H NMR and the same diastereomeric composition was found. Based on these results, we suppose that there is no need to assume catalytic activity of a cobalt–rhodium cluster in the amidocarbonylation step.

Conclusions

The steroidal α-amino acid derivatives prepared in this work are noteworthy as interesting pharmacologically active compounds. The main advantage of this synthesis is its atom-economic feature; this enables high regio- and stereoselectivities simultaneously, which is essential for a potential commercial application. One extremely important result is the excellent optical yield that was achieved, and attributed to the induction effect of the substrate. In the case of vinyl-estrone as starting material, our data do not support the cluster theory.

EXPERIMENTAL

{[Rh (nbd) Cl]$_2$} (nbd = 1,5-norbornadiene) was prepared according to the literature.[18] Dioxane was dried over sodium and distilled under argon. Amides were purchased from Aldrich. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (*Method A*) and DMF (*Method B*) on a Varian Unity 300 (Palo Alto, CA) spectrometer at 300 MHz and 75.5 MHz respectively. Gas–liquid chromatographic (GLC) analyses were performed on a Shimadzu GC-14A gas chromatograph fitted with a 5 m HP-1 column. Gas chromatography–mass spectroscopy (GC–MS) measurements were run on a Hewlett Packard 5971A GC-MSD. Infrared (IR) spectra were recorded in KBr pellets on a Specord-IR 75 instrument.

All manipulations were performed under argon using standard inert techniques.

General procedure

Method A

In a typical procedure a mixture of the steroid (1.5 mmol), {[Rh (nbd) Cl]$_2$} (17.4 mg, 0.0375 mmol), the phosphine ligand (0.15 mmol) and 3 mmol of amide in dioxane (10 ml) was transferred under argon into a 30 ml stainless steel autoclave. The autoclave was pressurized to 120 bar with CO:H_2 (1:1), placed into an oil bath, heated to 120 °C and stirred magnetically for 48 h at this temperature. The reaction was followed by GLC. Chromatography on silica gel with different eluents (hexane, benzene, ethyl acetate, acetone) yielded the desired compounds. The isolated products (**I, II, V**) were characterized by IR, MS, and various NMR techniques, including ^{2}D NMR experiments.

Method B

In a typical hydroformylation–amidocarbonylation experiment, a mixture of the steroid (1.5 mmol), {[Rh (nbd) Cl]$_2$} (17.4 mg, 0.0375 mmol), $Co_2(CO)_8$ (0.0375 mmol), the phosphine ligand (0.15 mmol) and 3 mmol of amide in dioxane (10 ml) was transferred under argon into a 30 ml stainless steel autoclave. The autoclave was pressurized with carbon monoxide (80 bar) and hydrogen (50 bar), placed in an oil bath, heated to 120 °C and stirred magnetically for 48 h at this temperature. Then, the apparatus was cooled and gasses were carefully purged out. A 5% aqueous sodium carbonate solution (10 ml) and ethyl acetate (30 ml) were added to the reaction mixture. The water layer was separated and the organic layer extracted with water and the water extract combined with the water layer. Then, the aqueous solution was acified with phosphoric acid and extracted with ethyl acetate (4 × 40 ml). The extract was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give the desired compound (**III**). The isolated products were characterized by IR, MS, and various NMR techniques, including ^{2}D NMR experiments. In some cases, detection by GLC of the methylated products was possible.

Characterization of the products

*16-(Acetamido-methylidene)-5α-androstane (**I**; R^1 = R^2 = H; R^3 = CH_3)*

^{1}H NMR ($CDCl_3$): 0.74 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); 2.05 (s, 3H, COCH_3); 6.66 (m, 1H, =CH—NH).

^{13}C NMR ($CDCl_3$): 12.2 (19-CH_3); 17.4 (18-CH_3); 20.7 (C-11); 22.1 (C-2); 23.2 (CO—CH_3); 26.7 (C-3); 28.8 (C-6); 28.9 (C-4); 29.0 (C-15); 32.3 (C-7); 35.3 (C-8); 36.3 (C-10); 38.2 (C-12); 38.6 (C-1); 40.5 (C-13); 46.6 (C-17); 46.9 (C-5); 53.8 (C-14); 54.7 (C-9), 115.3 (=CH—NH); 124.1 (C-16); 166.5 (CO).

IR [KBr, ν (cm^{-1})]: 1654 (CO); 1510 (C=C); 3310 (NH); 1450 (δ_{NH}).

MS: 329 (M^+), 314 ($M^+ - CH_3$), 270, 255; m.p. = 255 °C.

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*16-(Benzylamido-methylidene)-5α-androstane (**I**; $R^1 = R^2 = H$; $R^3 = -C_6H_5$)*

^{1}H NMR ($CDCl_3$): 0.75 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); 6.90 (m, 1H, =C*H*−NH); 7.5 (m, 5H, Ph).

^{13}C NMR ($CDCl_3$): 12.2 (19-CH_3); 17.4 (18-CH_3); 20.7 (C-11); 22.1 (C-2); 26.7 (C-3); 28.9 (C-6); 29.0 (C-4); 31.4 (C-15); 32.3 (C-7); 35.4 (C-8); 36.3 (C-10); 38.2 (C-12); 38.6 (C-1); 40.6 (C-13); 40.7 (C-10); 38.2 (C-12); 38.6 (C-1); 40.6 (C-13); 40.7 (C-10); 46.8 (C-17); 46.9 (C-5); 53.8 (C-14); 54.7 (C-9); 115.9 (=*C*H−NH); 125.1 (C-16); 128.2 (C-4′); 128.6 (C-3′); 131.6 (C-2′); 134.2 (C-1′); 163.6 (CO).

IR [KBr, ν (cm^{-1})]: 1650 (CO); 1505 (C=C).

MS: 391 (M^+), 376 ($M^+ - CH_3$), 270, 255, 105 (−CO−C_6H_5), 77 (−C_6H_5); m.p. = 274 °C.

*16-(Phenylacetamido-methylidene)-5α-androstane (**I**; $R^1 = R^2 = H$; $R^3 = -CH_2-C_6H_5$)*

^{1}H NMR ($CDCl_3$): 0.75 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); 3.6 (s, 2H, CO−CH_2); 6.61 (d, 1H, =C*H*−NH); 6.50 (d, 1H, =CH−N*H*); 7.4 (m, 5H, Ph).

^{13}C NMR ($CDCl_3$): 12.2 (19-CH_3); 17.4 (18-CH_3); 20.6 (C-11); 22.1 (C-2); 26.7 (C-3); 28.3 (C-6); 28.9 (C-4); 29.0 (C-15); 32.2 (C-7); 35.3 (C-8); 36.3 (C-13); 38.2 (C-12); 38.6 (C-1); 40.5 (C-13); 40.7 (C-10); 43.6 (−CO−*C*H_2); 46.6 (C-17); 47.0 (C-5); 53.7 (C-14); 54.7 (C-9); 115.0 (=*C*H−NH); 125.0 (C-16); 127.5 (C-4′); 129.0 (C-3′); 129.4 (C-2′); 134.6 (C-1′); 167.3 (CO).

IR [KBr, ν (cm^{-1})]: 1650 (CO); 1505 (C=C).

MS: 405 (M^+), 286 ($M^+ - C_6H_5-CH_2-CO-$), 270, 255, 207, 91; m.p. = 135 °C.

*3β-Hydroxy-16-(acetamido-methylidene)-5α-androstane (**I**; $R^1 = -OH$; $R^2 = H$; $R^3 = -CH_3$)*

^{1}H NMR ($CDCl_3$): 0.74 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); 2.0 (s, 3H, CO−CH_3); 3.58 (m, 1H, 3-CH); 6.63 (m, 1H, =C*H*−NH).

^{13}C NMR ($CDCl_3$): 12.2 (19-CH_3); 18.2 (18-CH_3); 21.2 (C-11); 23.2 (C-22); 28.5 (C-6); 31.2 (C-2); 31.4 (C-7), 32.1 (C-15); 35.3 (C-8); 35.5 (C-10); 36.9 (C-1); 38.0 (C-4); 38.4 (C-12); 40.6 (C-13); 43.8 (C-17); 44.7 (C-5); 53.7 (C-14); 54.3 (C-9); 71.1 (C-3); 115.7 (=*C*H−NH); 148.2 (C-16); 166.5 (CO).

IR [KBr, ν (cm^{-1})]: 1650 (CO); 1505 (C=C); 3310 (NH); m.p. = 120 °C.

*16-(Acetamido-methylene)-5α-androstane (**II**; $R^1 = R^2 = H$; $R^3 = -CH_3$)*

^{1}H NMR ($CDCl_3$): 0.74 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); 2.0 (s, 3H, COCH_3); 3.15 (m, 2H, −CH_2−NH).

^{13}C NMR ($CDCl_3$): 170.1, 169.9 (CO); 55.2, 55.1 (C-9); 54.8, 54.7 (CH_2−NH); 53.5, 47.4 (C-14); 47.3 (C-5); 46.6, 46.4 (C-16); 46.2, 44.4 (C-17); 41.5, 40.6 (C-13); 39.7 (C-1); 39.1, 39.0 (C-12); 36.3 (C-10); 35.6, 35.3 (C-8); 32.9, 32.8 (C-7); 30.6 (C-4); 30.3 (C-6); 29.2, 29.3 (C-15); 27.1 (C-3); 23.7, 23.6 (CO−*C*H_3); 22.5 (C-2); 21.0, 20.9 (C-11); 18.4, 20.2 (C-18); 12.6 (C-19).

MS: 331 (M^+), 316 ($M^+ - CH_3$), 281, 257, 217, 207, 74, 60.

*N-Acetyl-α-(5α-androsta-16-yl)-glycine (**III**; $R^1 = R^2 = H$; $R^3 = -CH_3$)*

^{1}H NMR (DMF): 0.74 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); 4.4 (q, 1H, 20α-CH); 4.25 (m, 1H, 20β-CH); 2.6 (m, 1H, 16-CH); 1.98 (s, 3H, −CO−CH_3).

^{13}C NMR (DMF): 12.0 (19-CH_3); 17.7, 17.8 (18-CH_3); 20.7 (C-11); 22.1, 22.2 (CO−CH_3); 21.9 (C-2); 26.8 (C-3); 28.9, 29.0 (C-15); 32.3, 32.5 (C-7); 35.7, 35.9 (C-8); 36.4 (C-10); 37.4 (C-4); 37.7 (C-6); 38.3 (C-1); 38.5, 38.8 (C-12); 40.6 (C-13); 41.2, 41.4 (C-16); 44.0, 44.8 (C-17); 47.2 (C-5); 53.5, 53.8 (C-14); 55.0, 55.1 (C-9); 56.2, 56.3 (C-20); 170.0, 170.1 (CO); 173.7, 173.77 (COOH).

IR [KBr, ν (cm^{-1})]: 1700 (COOH); 1630 (C=O); 1550 (δ_{NH}); 3345 (NH).

MS: 376, 358, 330, 257, 117, 99, 91, 79, 67; m.p. = 140–142 °C.

*N-Phenylacetyl-α-(5α-androsta-16-yl)-glycine (**III**; $R^1 = R^2 = H$; $R^3 = -CH_2-C_6H_5$)*

^{1}H NMR (DMF): 0.74 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); 4.4 (q, 1H, 20α-CH); 4.25 (m, 1H, 20β-CH); 2.6 (m, 1H, 16-CH); 7.35 (m, 5H, Ph).

^{13}C NMR (DMF): 12.0 (19-CH_3); 17.7, 17.8 (18-CH_3); 20.9, 21.0 (C-11); 22.54 (C-2); 27.1 (C-3); 28.7, 29.2 (C-15); 29.41 (C-6); 29.44 (C-4); 32.4, 32.5 (C-7); 35.6, 35.7 (C-8); 36.6 (C-10); 38.2 (C-1); 38.7, 38.8 (C-12); 39.0, 39.1 (C-16); 41.5, 41.6 (C-13); 47.3 (C-5); 47.4, 47.5 (C-17); 53.8, 54.1 (C-14); 55.1, 55.2 (C-9); 56.2, 56.3 (C-20); 128.65, 128.67 (C-1′); 128.7, 128.8 (C-4′); 129.7, 129.8 (C-3′); 137.36, 137.39 (C-2′); 171.2, 171.3 (CO); 173.8, 173.9 (−COOH).

IR (KBr, ν [cm^{-1}]): 1700 (COOH); 1630 (C=O); 1550 (δ_{NH}); 3345 (NH).

GC-MS (for the methylated product): 465, 406, 330, 257, 207, 91; m.p. = 105 °C.

*N-Acetyl-α-(3β-hydroxy-5α-androsta-16-yl)-glycine (**III**; $R^1 = -OH$; $R^2 = H$; $R^3 = -CH_3$)*

^{1}H NMR (DMF): 0.74 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); 1.96 (s, 3H, −CO−CH_3); 3.48 (m, 1H, 3-CH); 2.6 (m, 1H, 16-CH); 4.25 (m, 1H, 20β-CH); 4.4 (q, 1H, 20α-CH).

^{13}C NMR (DMF): 12.4 (19-CH_3); 18.0, 18.1 (18-CH_3); 21.4, 22.0 (C-11); 22.2, 22.3 (CO−CH_3); 22.9 (C-6); 29.2, 29.3 (C-15); 31.9 (C-2); 32.0, 32.7 (C-7); 36.1, 36.2 (C-8); 37.6 (C-4); 38.7, 38.9 (C-16); 41.5, 41.7 (C-13); 44.2 (C-17); 45.3 (C-5); 54.0, 54.9 (C-14); 55.0, 56.7 (C-9); 70.4 (C-3); 170.1, 170.2 (CO); 173.9, 174.0 (−COOH).

MS: 392, 374, 346, 328, 273, 257, 161, 147, 135, 117, 99; m.p. = 158 °C.

*N-Acetyl-α-(3β-hydroxy-pregna-5-ene-20-one-16-yl)-glycine (**III**; $R^1 = -OH$; $R^2 = -CO-CH_3$; Δ^5; $R^3 = -CH_3$)*

^{1}H NMR (DMF): 0.68 (s, 3H, 18-CH_3); 0.98 (s, 3H, 19-CH_3); 1.98 (s, 3H, −NH−CO−CH_3); 2.13 (s, 3H, −CO−CH_3); 3.38 (m, 1H, 3-CH); 2.6 (m, 1H, 16-CH); 4.42 (m, 1H, β-

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C*H*(COOH)—); 4.64 (q, 1H, α-C*H*(COOH)—); 5.33 (d, 1H, 6-CH); 8.2 (d, 1H, NH).

^{13}C NMR (DMF): 14.2, 14.4 (18-CH_3); 19.7 (19-CH_3); 21.6, 21.9 (C-11); 28.01 (C-2); 29.1, 29.4 (C-7); 29.6, 29.8 (C-15); 30.4 (C-1); 31.0, 31.3 (—NH—CO—CH_3); 31.5 (CO—CH_3); 34.4 (C-4); 35.1, 35.4 (C-16); 35.7, 35.9 (C-8); 36.2 (C-10); 38.3, 38.9 (C-12); 39.3, 39.4 (C-9); 45.2, 45.5 (C-13); 55.0, 55.6 (C-14); 56.2, 57.0 (—CH(COOH)—); 70.7 (C-3); 71.4 (C-17); 121.0; 121.2 (C-6); 142.3, 142.4 (C-5); 170.86 (CO); 173.9 (COOH); 208.0, 208.9 (C-20). M.p. = 126 °C.

*N-Acetyl-α-(20(R)-3β,20β-dihydroxy-pregna-5-ene-16-yl)-glycine (**III**; $R^1 = -OH$; $R^2 = -CH(CH_3)OH$, Δ^5; $R^3 = -CH_3$)*

^{1}H NMR (DMF): 0.65 (s, 3H, 18-CH_3); 0.98 (s, 3H, 19-CH_3); 1.15 (d, 3H, —CH(OH)CH_3); 2.13 (s, 3H, CO—CH_3); 3.36 (m, 1H, 3-CH); 2.6 (m, 1H, 16-CH); 4.45 (m, 1H, β-C*H*(COOH)—); 4.65 (m, 1H, α-C*H*(COOH)—); 5.33 (d, 1H, 6-CH).

^{13}C NMR (DMF): 14.8, 14.9 (18-CH_3); 19.6 (19-CH_3), 21.0, 21.3 (C-11); 22.49, 22.54 (—CH(OH)CH_3); 22.6, 22.9 (—CO—CH_3); 30.6, 31.0 (C-15); 31.5, 31.9 (C-8); 32.2, 32.3 (C-2); 32.5, 32.7 (C-7); 34.6, 34.9 (C-16); 36.02 (C-10); 37.08, 37.9 (C-1); 38.1, 38.3 (C-12); 42.38, 42.43 (C-4); 43.28, 43.82 (C-13), 50.59, 50.72 (C-9); 54.1 (C-14); 67.32 (C-17); 71.18 (C-3); 56.6, 56.7 (—CH(COOH)NH—); 61.8 (—CH(OH)CH_3); 121.1, 121.2 (C-6); 142.1, 142.2 (C-5); 170.6, 170.7 (CO); 174.3, 174.4 (COOH).

N-Acetyl-α-amino-β-(estron-3-yl)-butyric acid

^{1}H NMR ($CDCl_3$): 0.88 (s, 3H, 18-CH_3); 1.21 (s, CH_3—CH); 2.05 (s, 3H, CH_3—CO); 3.26 and 3.48 (m, 1H, CH_3—C*H** for diastereomer pairs); 4.51 and 4.77 (m, 1H, HOOC—C*H** for diastereomer pairs); 8.15 (d, 1H, NH).

Acknowledgements

The authors thank Z. Tuba and S. Mahó (Chemical Works of Gedeon Richter Ltd) for the steroids, G. Szalontai (University of Veszprém) for carrying out the NMR measurements. This work was supported by the Hungarian National Science Foundation (OTKA grants T 020185, T 034328).

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