Tetrahedron Vol. 43, No. 9, pp. 2129 to 2134, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00
Pergamon Journals Ltd.

SYNTHESIS OF BRIDGED STEROIDS WITH A BICYCLO [3.3.1.] NONANE RING A SYSTEM.

MARIAN KOCÓR [x] and BEATA BERSZ[xx]

Institute of Organic Chemistry, Polish Academy of Sciences,
ul. Kasprzaka 44/52 01-224 Warszawa, Poland

(*Received in UK 2 December* 1986)

Abstract - A synthesis of new groups of bicyclic steroids with a bicyclo [3.3.1.] nonane ring A system is described. The insertion of an additional ring is performed by means of the Michael addition of ethyl acetoacetate to 17β - propionoxyandrosta - 1,4,6-triene-3-one (1), followed by an aldol condensation of intermediate 17β - propionoxy-1 -(1'ξ -carboxyethylo-2'-oxopropano)-androsta-4,6-diene-3-one (2) to give 17β - propionate of 1α(1'), 3α (3') - (1'ξ -carboxyethylo-2'-oxopropano)-androsta-4,6-diene-3β , 17β - diol (3). Among derivatives of 3 an oxaadamantane steroid (1-oxatricyclo [3.3.1.1^{3,7}]nonane ring A system): 17β-propionate of 1α (1'), 3α (3')-propano-2'5α - epoxyandrosta-3β , 17β -diol (8) was obtained from 5a, 6a, and 7a. The synthesis of 8 provides the example of an intramolecular addition of a hydroxyl group to a double bond in a neutral medium. Hydrogenating conditions and a favorable stereochemistry seem necessary for this reaction.

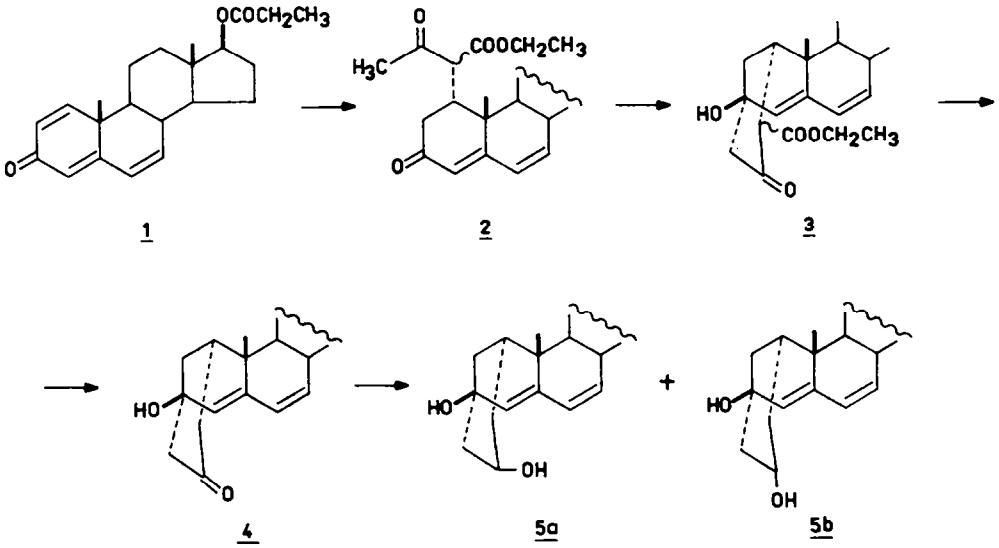
Among bridged steroids those with a bridged D-ring have been most frequently studied[1], some attention has been given also to steroids with a bridge connecting rings A and B [2].Steroids with a carbon - bridged ring A are much less represented in the literature. A meaningful contribution to the research in this area was made by Yates et al.[3] by obtaining steroids with a bicyclo [2.2.1] heptane ring A system and by Nagata et al. through the syntheses of bicyclo [3.2.1] octane [4] and bicyclo [2.2.2] [5] octane ring A systems. In the process of the investigation of the reactivity of steroidal 3-oxo-1,4,6-trienes carried in our group we have already introduced a bridged ring steroid with the ring A system of a bicyclo[2.2.2.]octane [6]. Now we would like to present the synthesis of a new group of bridged steroids with a bicyclo [3.3.1] nonane ring A system as well as a steroid with the oxaadamantane (1-oxatricyclo[3.3.1.1.^{3,7}]nonane) ring A system. During the study [7] of an addition of various Michael reagents to steroidal 3-oxo-1,4,6-trienes, it was observed that the cyclic 17α -methylo-1α(1'),3α(3')-(1'ξ -carboxyethylo-2'-oxopropano-androsta-4,6-diene-3β, 17β-diol is formed in the reaction of 17α -methylo-3-oxoandrosta-1,4,6-triene-17β-ol with ethyl acetoacetate. Our study of the reaction of 1 with ethyl acetoacetate led us to a conclusion that this reaction could be a convenient starting point in the synthesis of a new group of A-bicyclic steroids with an A'-ring attached to the steroidal skeleton in position 1 and 3. The reaction of 1 with ethyl acetoacetate in t-BuOH at 30°C in the presence of a tenfold excess of t-BuOK afforded product 3 in a 96% yield. The presence in 3 of the 4,6-diene system was confirmed by the UV spectrum (231, 237.5, 246nm). The reaction mechanism shown in scheme I was verified when intermediate 2 was isolated and subsequently transformed into 3.

---

[x] Deceased on 24 March 1980

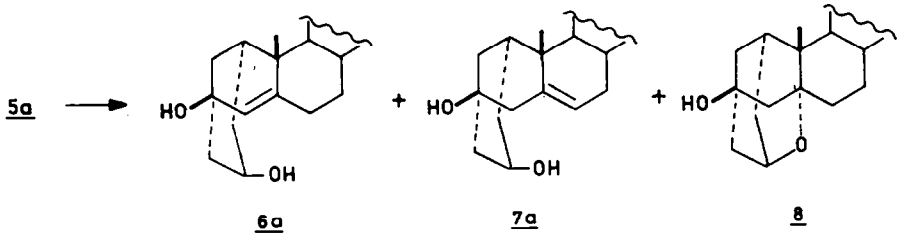
[xx] On Ph.D. fellowship in 1975-1979

We found that the highest yield of 2 (50%) was obtained when 1 eq of t-BuOK at room temp. was used in the reaction. An excess of t-BuOK leads to the aldol condensation converting 2 into 3, while in the presence of amounts of t-BuOK smaller than 1 eq, the conversion of substrate 1 drops below 50%. The decarboxylation of 3 according to the procedure of Crapcho and Lovell [8] gave product 4 in a 60% yield. The carbonyl group in ring A' of 4 was then reduced by using sodium borohydride in wet THF. The reaction afforded, in a 87% yield, the epimeric alcohols 5a and 5b in a 5:2 ratio. When bulky hydrides, like lithium-tri-sec-butylo borohydride (L-selectride) or lithium tri-t-butoxyaluminium hydride, were used in the reduction of 4, only product 5a was obtained (100%). Further experiments (see below) led to the following absolute configuration assignments: 2'R for the epimeric alcohol produced in excess (5a), and 2'S for the other (Scheme I).



Scheme I

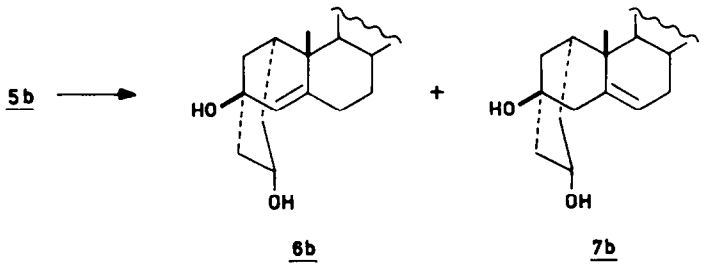
Hydrogenation of 5a on Pt catalyst in ethanol ceased after 1 eq of H_2 was consumed; products: 6a (38%) and 7a (40%), and 8 (8%) were obtained (Scheme II).



Hydrogenation conditions	Yield		
Pt - EtOH	39 %	40 %	8 %
Pd - EtOH	10 %	10 %	70 %
Pt - AcOH	0 %	0 %	100 %

Scheme II

The ^{1}H NMR spectrum contains a singlet (1H) at 5.44 ppm, corresponding to the olefinic proton at C-4. In the case of 7a a characteristic multiplet, (1H), appears at 5.56 ppm, this corresponds to the olefinic proton at C-6. Hydrogenation of 5a on Pt catalyst in glacial HAc afforded oxa-adamantano steroid 8 in a quantitative yield. No signals of olefinic protons were found in the ^{1}H NMR spectrum of 8. However, the addition of only one H_2 molecule to 5a was confirmed by the elemental analysis and mass spectroscopy. The mass spectrum of 8 deuterated in CH_3OD indicated the presence of only one hydroxyl group in 8. The ^{13}C NMR spectra (NBD, SEFT, SFORD) of 8 confirmed the assigned number of primary, secondary, tertiary and quaternary carbon atoms, and excluded the presence of a tetrasubstituted double bond, thus corroborating that an extra ring was formed. However, the assignment of all signals could not be made without additional studies. Appearance of 8 during thy hydrogenation of alcohol 5a proves the 2'R absolute configuration of alcohol 5a since only in the case of this epimer the C-3'—O—C-5 bridge can be formed.Accordingly, hydrogenation of alcohol 5b on Pt catalyst, either in ethanol or in HAc, affords a mixture of compounds 6b and 7b corresponding to the formal 1,2 - and 1,4 - additions of H_2 to the diene system (Scheme III).



Scheme III

A direct verification of the structure of compound 8 came from the X-ray diffraction study of a crystal of 8 performed by Duax et al.[9] This completes the proof of the α-orientation of the A' ring and the absolute configuration at C-2' in compounds 5a and 5b. Duax et al. found two different conformations of molecule 8 in the crystal (Fig. 1).

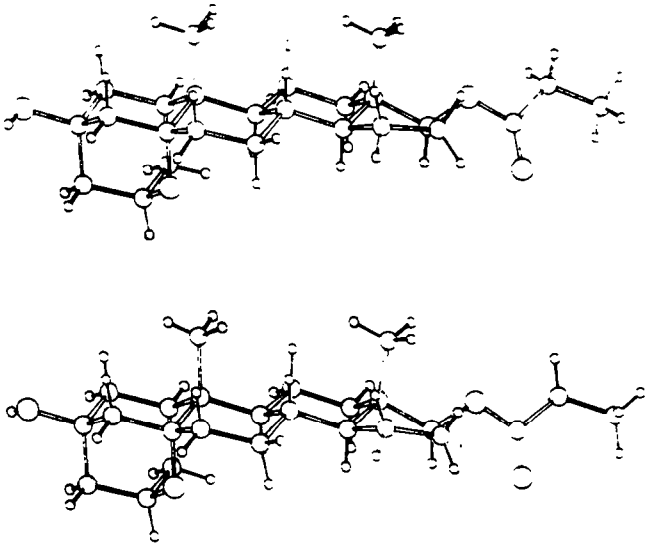
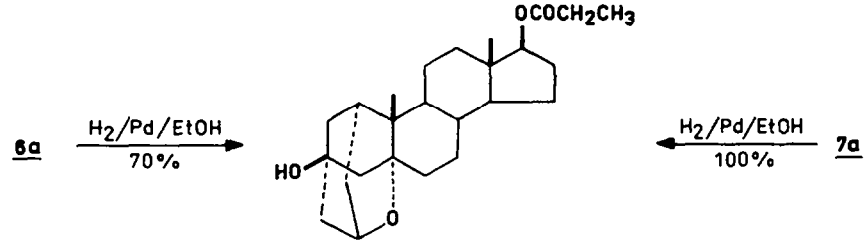


Fig. 1

Since the formation of a tetrahydropyran ring during the catalytic hydrogenation of a hydroxy olefin (as in the reaction 5a→8 seems rather uncommon, additional experiments were carried out. 5a resisted any changes on treatment with glacial HAc. Hydrogenation of 5a at Pd (10%/C) in ethanol at atmospheric pressure yielded oxaadamantano steroid 8 (70%) accompanied by compounds 6a (10%) and 7a (10%), (Scheme II). 6a and 7a subject to the above conditions both afforded 8 with 70% and 100% yield, respectively; (Scheme IV), it should be noted that no hydrogen absorption occurred in this case. Interestingly, no changes of 6a and 7a were observed in the absence of H_2.



8

Scheme IV

The above experiments indicate that an intracmolecular addition of a hydroxyl group to a double bond may take place upon hydrogenating conditions: H_2+catalyst+neutral medium. It seems that a necessary condition for this reaction is a favorable stereochemistry leading to a strainless product as illustrated by the conversion of 5a, 6a, and 7a into 8. To our best knowledge such an addition has not yet been recorded in the literature.

EXPERIMENTAL

General. The ^{1}HNMR spectra were obtained in $CDCL_3$ with a Jeol YNM-4-H-100 Spectrometer (100 MHz) or AC-200 Brucker spectrometer (200 MHz) and reported in δ(ppm) from Me_4Si. The ^{13}C NMR spectrum was recorded in $CDCl_3$ and reported in δ(ppm) from Me_4Si, on a AC-200 Brucker spectrometer. The IR spectra were carried out with a Beckmann IR 4240 spectrophotometer. The mass spectra (MS) were obtained on a LKB 2091 spectrometer (at 70 eV). High-resolution mass spectra (MS HR) were recorded on a Varian MAT 711 spectrometer. M.ps. measured in a Kofler hot bench are uncorrected. Microanalyses were performed on Perkin-Elmer 240 and Hewlett-Packard 185 units. Symbols:s-singlet, d - doublet, t - triplet, q - quartet, m - multiplet, were applied in the description on the ^{1}HNMR spectra. Symbols: 1° - primary, 2° - secondary, 3° - tertiary, 4° - quaternary carbon atom were used in the description of the ^{13}C NMR spectrum. In the description of the IR and MS spectra, only the most intense and/or structurally most important peaks were given. For column chromatography silica gel Merck 230-240 mesh or MN 100-200 mesh was used. TLC was performed on plastes coated with a 0.25 mm layer of silica gel (Merck 60F - 254). t-BuOH and benzene were distilled from CAH_2. Extracts were dried over $MgSO_4$.

17β-propionate of 1α(1'),3α(3')-(1'β-carboxyethylo-2'-oxopropano)-androsta-4,6-diene-3β,17β-diol (3):

Ethyl acetoacetate (16 ml, 126 mmol) followed by t-BuOK (40 mmol, 1.56 g K in 43 ml t-BuOH) was added to a solution of 17β-propionoxynadrosta-1,4,6-triene-3-one (2) (1.43 g, 4.2 mmol) in dry t-BuOH (150 ml). The reaction mixture was left to stand for 12 hrs at 30°. Water was added to the postreaction mixture and the product was extracted with ethyl acetate. The organic layer was washed with water, and aq. sat. $(NH_4)_2SO_4$, then concentrated in vacuo to give 1.9 g (96%) of the compound 3 (oil); IR ($CHCl_3$) ν max: 3625 (OH), 1720 (ketone), 1735 (ester) cm^{-1}; UV : 231, 237.5,246 nm (diene 4,6); ^{1}H NMR: 5,83 (dd, 1H, C-7-H, J_{7-6}=10Hz); 5.58 (d, 1H, C-6-H,J_{6-7}=10Hz); 5,25 (s, 1H, C-4-H); 4.65 (t, 1H, C-17-H,J_{17-16} = 7Hz); 4.22 (q, 2H, COO-CH_2-CH_3 J = 7Hz); 3.33 (broad s, 1H, C-1'-H); 1.32 (t, 3H, COO-CH_2-CH_3, J = 7 Hz), 1.20 (s, 3H, C-19-H); 0.90 (s, 3H, C-18-H); MS HR (m/e): Found: 470.2687, Calc. for $C_{28}H_{38}O_6$: 470.2668.

17β-propionoxy-1α(1'β-carboxyethylo-2'-oxopropano)-androsta-4,6-diene (2):

Ethyl acetoacetate (0.5 ml, 4 mmol) followed by t-BuOK (11.6 mg, 0.1 mmol) was added to a solution of 1 (46.8 mg, 0.14 mmol) in dry t-BuOH (5 ml). The reaction mixture was left to stand for 96 hrs at room temperature. The postreaction mixture was treated similarly as in the case of the synthesis of compound 3. The product was separated from substrate 1 by chromatography on silica gel (hexane - ethyl acetate, 9.5 : 0.5) 20 mg (43%) of substrate 1 and 29 mg (43%) of compound 2, mp. 174-176° (acetone) were obtained: IR ($CHCl_3$) ν max: 1735, 1720, 1660, 1625 cm^{-1}, UV: 278 nm; ^{1}H NMR (400 MHz) : 6.12 (s, 2H, C-6-H and C-7-H); 5.55 (s, 1H, C-4-H), 4.74 (t,

J = 7Hz, 1H, C-17-H) 4.05 (dq, 1H, J_{gem} = 10 Hz, J_{vic} = 6 Hz, O-$\underline{CH_2}$-CH_3), 3.92 (dq, 1H, J_{gem} = 10 Hz, J_{vic} = 6 Hz, O-$\underline{CH_2}$-CH_3)3.43 (d, J = 2 Hz, 1H, C-1'-H). 3.03 (dd, J_{1-2} = 6 Hz, J_{gem}=2Hz, 1H, C-1-H); 2.84 (dd, J_{gem} = 19 Hz, J_{vic} = 6 Hz, 1H, C-2-H); 2.67 (d, J_{gem} = 19 Hz, 1H, C-2-H); 2.35 (q, J = 6 Hz, 2H, $\underline{CO-CH_2}$-CH_3); 2.24 (m, 1H, C-8-H); 2.19 (s, 3H, $\underline{CH_3}CO$); 1.25 (s, 3H) and 0.90 (s, 3H) - the angular methyl groups; MS (m/e) : 470 (M^+, 12%), 340 (M^+-$CH_3COCH_2COOCH_2CH_3$,30% 325 (49%). Found: C: 71.39%, H: 8.35%, calc. for $C_{28}H_{38}O_6$ C: 71.46% H: 8.14%.

Transformation of 2 into 3

t-BuOK (46 mg, 0.4 mmol) was added to a solution of 2 (20 mg, 0.04 mmol) in dry t-BuOH (3ml) and the mixture was left to stand for 48 hrs at room temperature. Water was added to the post-reaction mixture and the product was extracted with ethyl acetate. The organic layer was washed with water, and aq. sat. $(NH_4)_2SO_4$, then concentrated in vacuo to give 20 mg (100%) of the compound 3, identical with the one previously prepared.

17β-propionate of 1α(1'), 3α(3')-(2-oxopropane)-androsta-4,6-diene-3β, 17β-diol (4):

A solution of the compound 3 (1.79 mg, 3.8 mmol) in DMSO (110 ml) containing water (1 ml) and NaCl (300 mg) was heated for 6 hrs at 155-165°. Water was added to the postreaction mixture and the products were extracted with ethyl acetate. After removal of the solvent the residue was chromatographed on silica gel (benzene - acetone, 95:5) to give 960 mg (65% yield) of the compound 4 mp 163-165° (MeOH); IR (KBr) ν max: 3500, 1735, 1720 cm^{-1}, UV: 232, 238, 247.5 nm (diene-4,6); ^{1}H NMR : 5.85 (dd, J_{7-6} = 10 Hz, J_{7-8} = 3 Hz, 1H, C-7-H); 5.55 (d, J = 10 Hz, 1H, C-6-H); 5.22 (s, 1H, C-4-H); 4.61 (t, J = 7 Hz, 1H, C-17-H); 1.09 (s, 3H) and 0.88 (s, 3H) - the angular methyl groups; MS (m/e): 398 (M^+, 25%), 341 (M^+ -CH_3CH_2CO, 100%). Found: C: 75.06%; H : 8.60%, calc. for $C_{25}H_{34}O_4$: C : 75.33%, H : 8.62%.

17β-propionate of (2'R) - 1α(1'), 3α(3')-(2'hydroxopropano)-androsta-4,6-diene-3β, 17β-diol (5a) and 17β-propionate of (2'S)-1α(1'),3α(3')-(2'-hydroxypropano)-androsta-4,6-diene-3β,17β-diol (5b):

Sodium borohydride (470 mg, 12.5 mmol) was added to a solution to the compound 4 (1g, 2.5 mmol) in THF (200 ml, 0.1% H_2O), and the mixture was stirred for 48 hrs at room temperature. Products were extracted with ethyl acetate, excess of $NaBH_4$ was decomposed with 20% acetic acid. The extract was washed with aq. sat. $NaHCO_3$. Products were separated into pure compounds by chromatography on silica gel (benzene - acetone 9:1), to give 590 mg (59%) of compound 5a, mp. 145-147° (acetone): IR ($CHCl_3$) νmax: 3600, 3450, 1735 cm^{-1}; UV : 238, 242.5, 250 nm; ^{1}H NMR : 5.95 (dd, J_{7-6} = 10 Hz, J_{7-8} = 3 Hz, 1H, C-7-H); 5.65 (d, J = 10 Hz, 1H, C-6-H); 5.50 (s, 1H, C-4-H); 4.62 (t, J = 7 Hz, 1H, C-17-H); 4.02 (m, 1H, C-2' -H); 2.25 (q, J = 6 Hz, 2H, CO-$\underline{CH_2}CH_3$); 1.12 (t, J = 6 Hz, 3H, CO-CH_2-$\underline{CH_3}$); 1.10 (s, 3H) and 0.90 (s, 3H) - the angular methyl groups; MS (m/e): 400 (M^+, 24%), 382 (M^+ -H_2O, 5%). Found: C: 75.03%; H: 9.19%; calc. for $C_{25}H_{36}O_4$ C: 74.95%, H: 9.08%; and 230 mg (23%) of compound 5b, mp. 91-93° (acetone): IR ($CHCl_3$) max: 3600, 3450, 1735 cm^{-1}; UV: 232, 241, 249 nm; ^{1}H NMR: 5.86 (dd, J_{7-6} = 10 Hz, J_{7-8} = 3 Hz, 1H, C-7-H); 5.54 (d, J_{6-7} = 10 Hz, 1H, C-6-H); 5.23 (s, 1H, C-4-H); 4.64 (t, J = 7 Hz, 1H, C-17-H); 3.65 (m, 1H, C-2'-H); 2.29 (q, J = 6 Hz, 2H, $CO\underline{CH_2}CH_3$); 1.04 (s, 3H) and 0.89 (s, 3H) - the angular methyl groups; MS (m/e) : 400 (M^+, 26%). Found: C: 75.10%; H : 9.24%, calc. for $C_{25}H_{36}O_4$: C : 74.95%, H : 9.08%.

17β-propionate of (2'R) - 1α(1'), 3α(3')-(2'-hydroxypropano)-4-androsten-3β, 17β-diol (6a) and 17β-propionate of (2'R)-1α(1'), 3α(3')-(2'-hydroxypropano)-5-androsten-3β, 17β-diol (7a):

PtO_2 (100 mg) in ethanol (2 ml) was hydrogenated for 50 min followed by addition of a solution of compound 5a (100 mg, 0.25 mmol) in ethanol (15 ml). The mixture was hydrogenated for 4 hrs at room temperature under atmospheric pressure. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The mixture of products was separated into pure compounds by chromatography on silica gel (benzene - acetone 95 : 5) to give 39 mg (39%) of compound 6a mp. 150-152° (acetone) : IR ($CHCl_3$) ν max: 3600, 3540, 1730 cm^{-1}; ^{1}H NMR: 5.44 (s, 1H, C-4-H); 4.61 (t, J = 7 Hz, 1H, C-17-H); 4.02 (m, 1H, C-2' -H); 1.16 (s, 3H) and 0.81 (s, 3H) - the angular methyl groups; MS (m/e): 402 (M^+, 28%), 384 (M^+-H_2O, 23%), 343 (27%) and 40 mg (40%) of compound 7a mp. 214-216° (acetone) : IR ($CHCl_3$) νmax: 3600, 3480, 1730 cm^{-1}; ^{1}H NMR: 5.56 (m, 1H, C-6-H); 4.62 (t, J = 7 Hz, 1H, C-17-H); 3.93 (m, 1H, C-2'-H); 1.16 (s, 3H) and 0.80 (s, 3H) - the angular methyl groups; MS (m/e): 402 (M^+, 34%), 384 (53%), 343 (21%), 341 (21%); HR MS (m/e): found: 402.2770, calc. for $C_{25}H_{38}O_4$: 402.2768, and 8 mg (8%) of compound 8 (see below).

17β-propionate of (2'S)-1α(1'), 3α(3')-(2'hydroxypropano)-4-androsten-3β, 17β-diol (6b) and 17β-propionate of (2'S)-1α(1'),3α(3')-(2'-hydroxypropano)-5-androsten-3β, 17β-diol (7b):

Hydrogenation of 5b (40 mg) according to the above procedure gave a mixture of 6b and 7b (40 mg). Separation of the mixture was not performed. The following signals were found in the ^{1}H NMR spectrum of this mixture: 5.25 (m, 1/2 H, C-6-H in 7b); 5.12 (s, 1/2 H, C-4-H in 6b), 4.61 (t, 1H, C-17-H); 3.70 (m, 1H, C-2' -H); 1.25 (t, 3H, $COCH_2\underline{CH_3}$); 1.12, 1.08, 1.06, and 0.8 - singlets of the angular methyl groups in 6b and 7b.

17β-propionate of 1α(1'), 3α(3')-propano-2', 5α-epoxyandrosta-3β, 17β-diol (8):

PtO_2 (200 mg) in acetic acid (4 ml) was hydrogenated for 50 min, followed by addition of a solution of compound 5a (100 mg, 0.25 mmol) in acetic acid (15 ml). The mixture was hydrogenated for 4 hrs at room temperature under atmospheric pressure. The catalyst was removed by filtration. Water was added to the filtrate and the product was extracted with $CHCl_3$. The organic layer was washed with aq. sat. $NaHCO_3$, then concentrated in vacuo to give 100 mg (100%) of compound 8, mp. 170-171° (acetone): IR ($CHCl_3$) ν max. : 3600, 1735 cm^{-1}; ^{1}H NMR : 4.59 (dd, J = 7.64 Hz, J=7.46 Hz, 1H, C-17-H); 4.27 (m, 1H, C-2-H); 2.28 (q, J = 7.60 Hz, 2H, CO-$\underline{CH_2}\underline{CH_3}$); 1.10 (t, J = 7.60 Hz,3H, CO-$CH_2\underline{CH_3}$); 0.97 (s, 3H) - protons of the angular methyl groups; ^{13}C NMR:assignment of the

signals corresponding to atoms C-11 - C-22 was based on analogical data for testosterone propionate [10]: 174.53 (C=O), 82.60 (3^{o}, C-17), 77.50 (4^{o}, C-3 or C-5), 70.38 (3^{o}, C-2'), 67.71 (4^{o},C-5 or C-3), 50.52 (3^{o}, C-14), 45.64 (2^{o},C-3' or C-4), 45.51 (2^{o}, C-4 or C-3'), 42.75 (4^{o}, C-13), 42.30 (3^{o}), 39.73 (2^{o}, C-12), 38.42 (4^{o}, C-10), 36.98 (2^{o}), 35.82 (3^{o}), 34.90 (3^{o}), 33.75 (2^{o}), 29.66 (2^{o}), 27.87 (2^{o}, C-16 or C-21), 27.59 (2^{o}, C-16 or C-21), 25.86 (2^{o}), 23.56 (2^{o}, C-15), 19.38 (2^{o}, C-11), 17.43 (1^{o}, C-19), 12.04 (1^{o}, C-18), 9.31 (1^{o}, C-22). MS (m/e): 402 (M^{+}, 58%), 387 ($M^{+}-CH_3$, 70%); MS (m/e) (CH_3OD) : 403 (M^{+},21%),388 ($M^{+}-CH_3$, 24%). Found: C: 74,36%, H:9.72%, calc. for $C_{25}H_{38}O_4$ C : 74.57% H : 9.53%.

Hydrogenation of 5a on Pd - catalyst.

Pd 10%/C (20 mg) and 5a (40 mg) in ethanol (2ml) was hydrogenated at room temperature under atmospheric pressure. 1 eq of H_2 was absorbed during 4 hrs of stirring. The catalyst was removed by filtration, the filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (benzene - ethyl acetate 9:1) to give 4 mg (10%) of 6a, 4 mg (10%) of 7a and 28 mg (70%) of 8.

Hydrogenation of 6a

Hydrogenation of 6a (20 mg) on Pd 10%/C (10 mg) in ethanol was conducted in an analogous manner to the previously described procedure. No hydrogen was absorbed during 3 hrs of stirring. The catalyst was removed by filtration, the filtrate was concentrated and the residue was chromatographed on silica gel (benzene - ethyl acetate 9:1) to give 14 mg (70%) of 8 identical with the one previously prepared.

Hydrogenation of 7a

Hydrogenation of 7a (20 mg) according to the above procedure gave 20 mg (100%) of 8, identical with the one previously prepared. (No hydrogen was absorbed during 3 hrs of stirring).

Acknowledgements:

One of the authors (B.B.) would like to express her gratitude to Dr. W.L. Duax and Dr. Z.Wawrzak for performing the crystal structure study of the compound 8, and for sending the result prior to publication. B.B. wishes also to thank Prof. J.Wicha for his interest in the present work and for reading and commenting on the manuscript.

REFERENCES

1. A.J. Solo, J.N.Kapoor, and P.Hebborn, J.Med.Chem. 13, 751 (1970); A.J.Solo, J.N.Kapoor, ibid, 16, 270 (1973) and ref. cited therein; A.J.Solo, S.Eng, and B.Singh, J.Pharm.Sci. 62, 1471 (1973);C.G.Pitt, D.H.Rector, C.E.Cook, and M.C.Wani, J.Med.CHem, 22, 966 (1979)
2. J.R.Bull, L.M.Steer, and P.H. van Rooyen, J.Chem.Soc. Perkin Trans.I, 397, (1984) and ref. cited therein; A.C.Ghosh, B.G.Hazra and W.L.Duax, J.Org.Chem. 42, 3091, (1977); A.C.Ghosh, B.G.Hazra, I.Krupnielsen, M.J.Kane, D.Hawke, W.L. Duax, and C.M.Wecks, J.Org.Chem. 44, 683 (1979)
3. P.Yates and F.M.Walliser, Can.J.Chem. 54, 3508 (1976); F.M.Walliser and P.Yates, Chem.Comm. 1025, (1979); P.Yates and F.M.Winnik, Can.J.Chem. 59, 1641 (1981); S.P.Douglas, J.F.Sawyer and P.Yates, Tetrahedron Lett. 5955 (1985).
4. W.Nagata and M.Narisada, Chem.Pharm.Bull., 16, 867 (1968); W.Nagata, M.Narisada, and T.Wakabayashi, ibid 16, 875
5. W.Nagata, M.Narisada, T.Sugasawa, and T.Wakabayashi, ibid 16, 885
6. M.Kocór and W.Kroszczyński, Tetrahedron Lett. 5143, (1970)
7. T.Cynkowski, Ph.D. Thesis, 1974, Warsaw; for a similar Michael chemistry leading to a heterocyclic 1,3 adduct see: M.M. Campbell, V.B. Jigajinni, and R.H. Wightman, Tetrahedron Lett. 2455 (1979) (thanks are due to the referee for pointing out this reference to us).
8. A.P.Crapcho and A.J.Lovell, Tetrahedron Lett. 957 (1973), and ibid, 1091 (1974)
9. W.L.Duax, P.D.Strong, Z.Wawrzak, Z.Gałdecki, and P.Grochulski, Acta Cryst.C submitted for publication
10. A.Ejchart and L.Kozerski "Spektrometria magnetycznego rezonansu jądrowego ^{13}C", PWN, Warszawa 1981