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CONFIGURATIONAL ANALYSIS OF 16-METHYL-ANDROSTENE-5 DERIVATIVES†

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Abstract—The four possible isomers of 16-hydroxymethyl-androst-5-ene-3β,17-diol were converted into the corresponding 16-methyl analogues characterized by ^{13}C-NMR and ^{1}H-NMR spectra. This made possible the configurational correlation of 16-methylandrost-5-ene derivatives described in the literature.

The introduction of alkyl substituents at C-16 results in changes in the biological activity of several steroids. In the cortocoide series, the introduction of the C-16 methyl group enhances the activity of the mother compound.[1,2] In the case of other steroids, such as androstane, oestrane and the aldosterone antagonists, alkyl substitution at a similar site causes the reduction of hormone activity. This observation has become important recently, when the anti-hormone effect of 16-alkyloestrone,[3-5] and 16,16-dimethyl-4-oestrene-3-one was recognized.[6]

In the case of compounds with androstane skeleton, several methods are known suitable for the introduction of the C-16 methyl group. Julian *et al.*[7] started from 16 - methyleneandrost - 5 - ene - 3β - ol-17 - one - 3 - acetate (**1b**), and obtained 16 - methylandrost - 5 - ene - 3β - ol - 17 - one - 3 - acetate (**3b**) on hydrogenation in the presence of Raney nickel catalyst in the first step, while further hydrogenation yielded 16-methylandrost-5-ene-3β,17-diol - 3 - acetate (**13b**). On the basis of physical data, the products obtained (**3b** and **13b**) seemed to be homogeneous, but the C-16-methyl and C-17-hydroxyl functional groups were denoted as having undetermined configurations. Neumann *et al.*[8] started from **1a** and **1b** using Pd–C catalyst to obtain **3a** and **3b**. The C-16-methyl group in the substances obtained was also regarded as having undetermined configuration. They have stated, however, that the melting point of **3b** (143–146°) agrees with that is given by Julian *et al.* Sciaky[9] prepared **3a** by hydrogenation of **1a** in the presence of Pd–C and assigned first β configuration to the 16-methyl group. This assignation was based on two aspects. First, he assumed that the methylene group in the starting compound (**1a**) transforms into a β methyl owing to sorption at the surface of the catalyst. On the other hand, the physical data of the substance obtained by him (**3a**) agreed with the data established for the compound (**3a**) obtained on side-chain oxidation of 16β-methylpregn-5-ene-3β,17α,20-triol with HIO_4 (Fig. 1). Ruggieri *et al.*[10] prepared 16α- and 16β-methylpregn-5-ene-3β-ol-20 one of confirmed configuration by effecting a Grignard reaction between 5,16-pregnadiene-3β-ol-20-one and methyl iodide and addition with diazomethane with subsequent decomposition. Side-chain isomerization of 16β-methylpregn-5-ene-3β-ol-20-one is alkaline medium yielded 16β-methyl-17-iso-pregn-5-ene-3β-ol-20-one. The Baeyer–Villiger oxidation of the pregnane derivatives substituted in different manners yielded three (**11**, **12** and **13**) of the four possible isomers of 16-methylandrost-5-ene-3β,17-diol. At the same time, the Beckmann rearrangement of 16α- and 16β-methylpregn-5-ene-3β-ol-20-one resulted in 16α- and 16β-methylandrost-5-ene-3β-ol-17-one (**2a**, **3a**). In the reduction reaction with $NaBH_4$, their acetylated derivatives (**2b**, **3b**) behaved in a stereospecific manner yielding **11b** and **13b**.[11]

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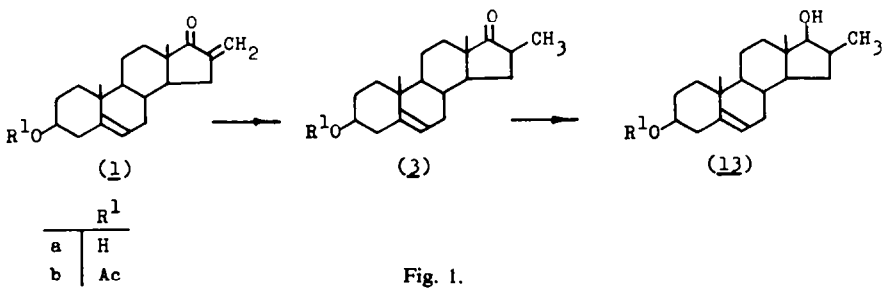


Fig. 1.

Recently Neef *et al.*[12] have pointed out that the 16-methyl-17-ketosteroids (**2a** and **3a**) show interconversion in an equilibrium reaction, but, as for the extent of this equilibrium, the opinions are rather divergent in the literature. Such a preparation method was therefore employed which yielded stereohomogeneous **2a** and **3a**, which also made possible the correction of the literature physical constants.

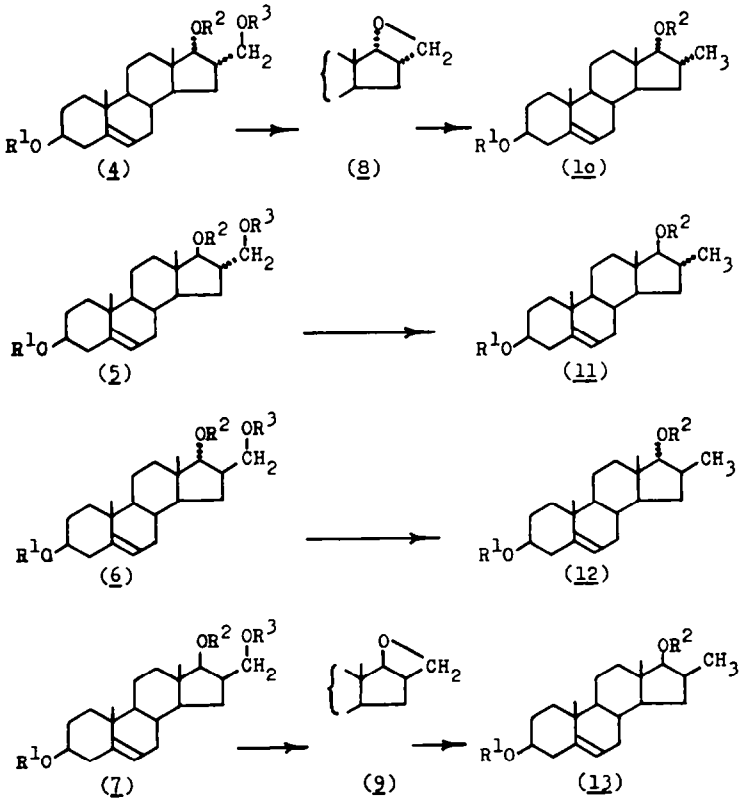
In the present work, the preparation of the four possible isomers (**10**, **11**, **12**, **13**) of 16-methylandrost-5-ene-3β,17-diol with confirmed configuration was aimed at, independently from the reaction paths described in the literature. This makes possible the configurational comparison of the isomers (**11**, **12**, **13**) prepared earlier by other methods, as well as the completion of the isomer series by compound **10**. The steric structures of the isomers prepared are confirmed by the ^{13}C-NMR and ^{1}H-NMR spectra.

In our earlier papers it was already reported that the reduction of 16-hydroxymethylene-17-keto- steroids with complex metal hydrides leads to a mixture of the isomers of corresponding 16-hydroxymethyl-17-hydroxy derivatives.[13-15] The four 16-hydroxymethyleneandrost-5-ene-3β,17-diol isomers (**4a**, **5a**, **6a**, **7a**) were converted into the corresponding 16 - p-toluenesulfonyloxymethylandrost - 5 - ene - 3β,17 - diol - 3,17 - diacetates (**4b**, **5b**, **6b**, **7b**). These were reduced into the corresponding 16 - methylandrost - 5 - ene - 3β,17 - diols (**10a**, **11a**, **12a**, **13a**) with $LiAlH_4$ in tetrahydrofuran. Under the conditions of the reduction reaction, **4b** and **7b** showed cyclisation into the steroid-oxetanes (**8** and **9**) condensed to the ring D in α and β position, respectively, described by us earlier,[16] in the first step, while further reduction resulted in their decomposition into the 16-methyl desired steroids (**10a** and **13a**). Since the reduction did not involve any chiral centre, the configuration of the compounds obtained agreed with that of the starting compounds with confirmed configuration (Fig. 2).

The preparation of **2b** and **3b** was achieved by the conversion of stereochemically homogeneous **11a** and **13a**. They were acetylated selectively to obtain **11b** and **13b** followed by a Jones oxidation to yield **2b** and **3b** (Fig. 3).

Hydrogenation of **1b** in the presence of both Pd–C and Raney nickel was reproduced according to the literature methods.[7,8] Hydrogenation was found to take place in two steps. The first, relatively fast process yields 16-methylandrost-5-ene-3β-ol-3-acetate (**3b**) being a homogeneous substance with a C-16 methyl group in configuration as shown by the ^{13}C-NMR spectrum. Further hydrogenation leads to the corresponding 16-methyl-17-hydroxy derivative being again a homogeneous substance with C-16 methyl and C-17 hydroxyl groups in β position (**13b**).

The position of isomers in the thin-layer chromatogram showed a characteristic picture. The most



	R^1	R^2	R^3
a	Ac	H	H
b	Ac	Ac	Ts

	R^1	R^2
a	H	H
b	Ac	H
c	Ac	Ac

Fig. 2.

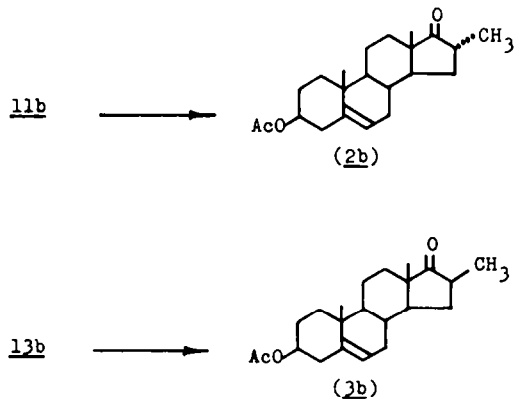


Fig. 3.

polar character was shown by the two *trans* isomers (**11, 12**), the *cis* isomers (**10, 13**) were found to be less polar (Table 3). This behaviour is in accordance with the mutual interaction of the C-16, C-17 and C-13 functional groups and agrees with the observations in the case of 16 - methoxymethylandrost - 5 - ene - 3β,17 - diol derivatives.[16] A further characteristic of the thin-layer chromatograms is that the isomers containing the 17α-hydroxyl group (**10, 12**) produce a bluish grey spot when detected with phosphoric acid, while those containing the 17β-hydroxyl group (**11, 13**) produce a brown spot under similar conditions.

The steric interaction between the functional groups of the isomers examined (**10c–13c** and **2b, 3b**) caused a characteristic shift in the ^{13}C-NMR spectrum (Table 1). The signals were assigned by employing the "off resonance" technique, using the data from earlier measurements[17] and literature data.[18] The correctness of the assignment of signals in the ^{13}C-NMR spectra of **10c-13c** was checked by the addition of Eu(dpm)$_3$ shift reagent. Owing to the pseudocontact interaction, complex formation took place at the C-3 and C-17 acetoxy groups. The assignment of configuration could be effected unambiguously on the basis of the appropriate configuration-sensitive signals (Fig. 4).

The determination of the configuration of the C-17 substituent in compound **10c–13c** was based on the chemical shift of carbon atoms at position (C-12 and C-18) in the ^{13}C-NMR spectra.[17] Owing to the γ interaction, the 17α substituent causes a high field shift of 5 ppm at the C-12 carbon atom, similarly, the 17β substituent causes a high field shift of 3–4 ppm at the C-18 carbon atom. The configuration of the C-16 substituents can be determined from the strong interaction of the *cis* C-16 and C-17 groups, which, opposite to the *trans* arrangement, causes a high field shift of 5 ppm at the C-17 signal. As a supplementary information, the γ interaction of C-17 substituents of *cis* position at the C-16 methyl group producing a high field shift of 4 ppm can also be used.

The following characteristic shifts in the ^{13}C-NMR spectra hold for the configuration assignment of the functional groups of 16-methylandrost-5-ene-3β,17-diol-3,17 diacetates (**10c–13c**) about $\pm$ 0.5 ppm): 17α

Table 1. ^{13}C NMR chemical shifts of 16-methyl-5-androstene derivatives[a]

	10c	11c	12c	13c	2b	3b	14b
C 1	37.0	36.9	37.0	36.9	36.9	36.8	37.1
C 2	27.7	27.7	27.7	27.7	27.6	27.6	27.8
C 3	73.8	73.8	73.8	73.8	73.6	73.6	73.8
C 4	38.1	38.0	38.1	38.1	38.0	38.0	38.1
C 5	139.6	139.7	139.6	139.7	139.8	139.8	139.5
C 6	122.4	122.1	122.3	122.2	121.8	121.8	122.6
C 7	32.0	31.3	32.1	31.6	30.7	30.9	32.1
C 8	32.0	31.5	31.6	31.1	31.3	31.0	32.1
C 9	49.8	50.0	49.7	50.0	50.2	50.2	50.3
C10	36.6	36.6	36.6	36.6	36.7	36.7	36.7
C11	20.3	20.4	20.2	20.4	20.2	20.2	21.1
C12	31.7	36.9	32.1	37.5	30.2	30.9	38.6
C13	47.5	44.0	44.4	42.9	48.0	47.7	40.5
C14	49.3	49.4	51.1	50.1	48.9	50.2	54.7
C15	33.8	32.4	34.8	32.9	31.7	31.8	25.6
C16	33.8	35.4	40.8	34.3	39.2	43.6	20.5
C17	83.2	89.1	88.4	83.5	222.7	222.9	40.2
C18	15.6	12.5	17.2	13.2	14.1	13.8	17.2
C19	19.3	19.3	19.3	19.3	19.3	19.3	19.3
3β-O-C=O	170.4	170.3	170.4	170.3	170.4	170.2	170.2
CH_3	21.4	21.3	21.4	21.4	21.3	21.3	21.3
16-CH_3	16.8	20.4	20.8	16.8	16.6	16.9	
17-O-C=O	170.8	171.1	170.7	171.0			
CH_3	20.9	21.1	21.2	20.9			

[a](δ, ppm from TMS).

Table 2. ^{1}H NMR chemical shifts of 16-methyl-5-androstene derivatives[a]

N°	Substituent			Chemical shifts								Coupling constants (Hz)	
	3	16	17	3	6	17	$16CH_3$	$18CH_3$	$19CH_3$	OH	OAc	$J_{16,17}$	J_{16,CH_3}
10a	βOH	α CH_3	α OH	3.5	5.3	3.5	1.02	0.8	1.05	1.7	-	6.0	7.0
11a	βOH	α CH_3	β OH	3.5	5.35	3.1	1.1	0.79	1.03	1.7	-	6.5	7.0
12a	βOH	β CH_3	α OH	3.5	5.35	3.42	1.05	0.75	1.00	1.55	-	≤1.0	7.0
13a	βOH	β CH_3	β OH	3.5	5.35	3.6	1.0	0.76	1.02	1.8	-	10	7.0
10c	βOAc	α CH_3	α OAc	4.6	5.45	4.90	1.00	0.85	1.02	-	2.05;2.1	5.5	7.0
11c	βOAc	α CH_3	βOAc	4.7	5.5	4.45	1.08	0.82	1.02	-	2.04;2.08	7.0	7.0
12c	βOAc	β CH_3	α OAc	4.65	5.45	4.45	1.2	0.85	1.05	-	2.05	≤1.0	7.0
13c	βOAc	β CH_3	βOAc	4.65	5.4	4.6	0.9	0.84	1.04	-	2.04;2.08	9.5	6.5
11b	βOAc	α CH_3	βOH	4.55	5.35	3.1	1.12	0.80	1.05	1.7	2.04	6.5	7.0
13b	βOAc	β CH_3	βOH	4.6	5.35	3.6	1.03	0.78	1.05	1.8	2.05	10.0	6.5
2b	βOAc	α CH_3	=O	4.55	5.4	-	1.12	0.9	1.05	-	2.05	-	7.0
3b	βOAc	β CH_3	=O	4.5	5.35	-	1.2	0.85	1.05	-	2.03	-	7.0

[a](δ, ppm from TMS).

Table 3.

No.	Formula Molecular weight	M.p., °C and Lit.m.p.	$[\alpha]_D$	R_f	Analysis, % Calcd./Found		Yield %
					C	H	
10a	$C_{20}H_{32}O_2$ (304.45)	232-234	-64° [a]	0.70 [e]	78.89 78.70	10.60 10.47	84.6
10c	$C_{24}H_{36}O_4$ (388.53)	137-139	-59°	0.65 [g]	74.19 74.33	9.34 9.45	96.3
11a	$C_{20}H_{32}O_2$ (304.45)	212-214 211-213 [b]	-61°	0.60 [e]	78.89 78.70	10.60 10.48	80.5
11b	$C_{22}H_{34}O_3$ (346.49)	138-140 135-137 [b]	-75°	0.40 [f]	76.26 76.38	9.89 9.73	37.5
11c	$C_{24}H_{36}O_4$ (388.53)	183-186 184-186 [b]	-109°	0.65 [g]	74.19 74.45	9.34 9.22	95.4
12a	$C_{20}H_{32}O_2$ (304.45)	275-278 221-223 [b]	-71°	0.55 [e]	78.89 78.72	10.60 10.49	92.5
12c	$C_{24}H_{36}O_4$ (388.53)	136-138 138-139 [b]	-47°	0.65 [g]	74.19 74.32	9.34 9.57	98.2
13a	$C_{20}H_{32}O_2$ (304.45)	185-187 186-188 [b]	-50°	0.65 [e]	78.89 78.58	10.60 10.43	87.8
13b	$C_{22}H_{34}O_3$ (346.49)	138-141 133-135 [b]	-60°	0.50 [f]	76.26 76.38	9.89 9.75	44.3
13c	$C_{24}H_{36}O_4$ (388.53)	170-172 172-174 [b]	-53°	0.65 [g]	74.19 74.38	9.34 9.25	97.5
2b	$C_{22}H_{32}O_3$ (344.48)	112-117 106-107 [c]	-13°	0.80 [f]	76.70 76.51	9.42 9.47	93.0
3b	$C_{22}H_{32}O_3$ (344.48)	139-141 140-143 [c]	+ 1°	0.60 [f]	76.70 76.81	9.42 9.48	90.1
14a	$C_{19}H_{30}O$ (290.45)	130-132 131 [d]	-51°	0.20 [g]	85.15 85.28	11.08 11.27	72.4
14b	$C_{21}H_{32}O_2$ (316.48)	95-96 91-93 [d]	-74°	0.85 [g]	79.60 85.77	10.20 10.34	97.6

[a]Ethanol; [b]Ref. 10; [c]Ref. 11; [d]Ref. 20; [e]acetone:benzene:petroleum ether (30:35:35); [f]methanol:benzene (1:99); [g]methanol:benzene (0.5:99.5).

substituent δ(C-18) = 16.5 ppm, δ(C-12) = 32.0 ppm; 17β substituent δ(C-18) = 13.0 ppm, δ(C-12) = 37.0 ppm; 16,17-*cis* substituent δ(C-17,) = 83.4 ppm, δ(C-16-methyl)-16.8 ppm; 16,17-trans substituent δ(C-17) = 88.8 ppm, δ(C-16-methyl) = 20.6 ppm.

In the ^{13}C-NMR spectra of two isomers (**2b** and **3b**) of 16 - methylandrost - 5 - ene - 3β - ol - 17 - one - 3 - acetate relatively small differences can be observed. Comparison with androst-5-ene-3β-ol-3-acetate (**14b**) carrying no substituent at ring D indicated that the presence of the C-17 keto group produces a significant γ interaction at C-12 and a smaller interaction at the C-18 carbon atoms, in both **2b** and **3b**. At the C-12 carbon atom, a high field shift of 8 ppm can be observed, while at C-18 this is only 3 ppm. The α methyl group adjacent to the C-17 ketone (**2b**) shows a high field shift of about 4 ppm, unlike the methyl group at the C-16 carbon atom (**3b**). The characteristic chemical shifts in the ^{13}C-NMR spectra of 16 - methylandrost - 5 - ene - 3β - ol - 17 - one isomers (**2b** and **3b**) are the followings: 16α-methyl-17-ketone: δ(C-16) = 39.2 ppm; 16β-methyl-17-ketone: δ(C-16) = 43.6 ppm.

The ^{1}H-NMR data also indicate that the configuration of the C-16 methyl isomers (**10c–13c**) can be determined unambiguously from the value of the $J_{16,17}$ coupling constant (Table 2). The constants show the following order: $J_{16\alpha H,17\beta H} < J_{16\beta H,17\beta H} < J_{16\beta H,17\alpha H} < J_{16\alpha H,17\alpha H}$ (the substituents represent a reversed order).

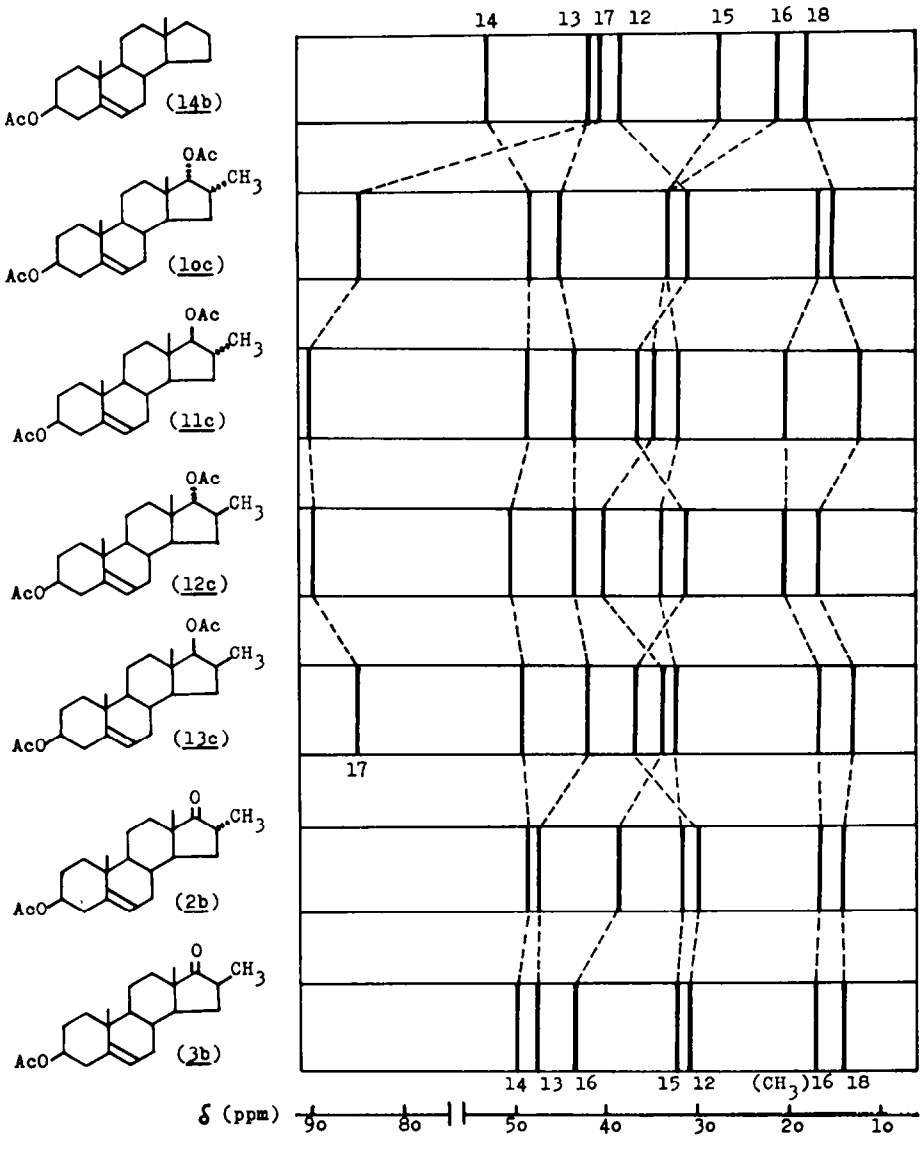


Fig. 4.

The value of the coupling constant ($J < 1.0$ Hz) in the 16β,17α-disubstituted isomers (**12c**) differs from that observed in the 16α,17α isomer (**10c**; $J = 5.5$ Hz). A higher value is found in the spectrum of the 16α,17β isomer (**11c**, $J = 7.0$ Hz), while the higher coupling constant in the series was produced by the 16β,17β isomer (**13c**, $J = 9.5$ Hz). This observation is in agreement with the rule observed in the case of the four possible isomers of C-16, C-17-disubstituted compounds with oestrane skeleton.[19]. The characteristic values of the coupling constants of C-16, C-17 isomers seem to be unaffected by ring A in the sterane skeleton.

EXPERIMENTAL

M.ps were measured on a Koefler block and are uncorrected. Specific rotation was measured with a Polamat-A polarimeter, at a concentration of $c = 1$ in chloroform. Other solvents used are indicated. Thin-layer chromatograms were obtained on Kieselgel G (Merck) layers of thickness of 0.5 mm. The following solvent mixtures were employed as developing agents: (I) methanol:benzene (0.5:99.5); (II) methanol:benzene (1:99); (III) acetone:benzene:petroleum ether (30:35:35). The chromatograms were detected by spraying with 50% phosphoric acid with subsequent heating at 100–120°C for 15 min. The R_f values were determined in UV light of 365 nm wavelength. In the column chromatographic separation procedures, Al_2O_3 of activity III–IV standardized according to Brockmann was used. Dimensions of the chromatographic column were: 25 × 2 cm, 50 g Al_2O_3.

The ^{13}C-NMR spectra were recorded with a PS 100/PFT 100 (JEOL-Tokyo) spectrometer coupled with a Nicolet (NIC 1085) computer at 25.15 MHz, using proton-noise decoupling at a flip angle of 45° and a repetition time of 3 s. The frequency with was 5000–6000 Hz, the digital resolution was 1.2–1.5 Hz. The ^{1}H-NMR spectra were recorded with a Jeol C-60 HL Tokyo instrument at 60 MHz. The spectra were recorded in both cases in $CDCl_3$ solutions using TMS as internal standard. Chemical shifts are given in ppm values.

16 - *Methylandrost* - 5 - *ene* - 3β,17 - *diol* (**10a**, **11a**, **12a**, *and* **13a**). *General method* 1. $LiAlH_4$ (1 g) was suspended in anhydrous tetrahydrofuran (50 mL) under cooling in ice and

a solution of 16 - p - toluenesulphonyloxymethylandrost - 5 - ene - 3β,17 - diol - 3,17 - diacetate (0.005 mol) (**4b**, **5b**, **6b**, **7b**)[14,16] in anhydrous tetrahydrofuran (50 mL) was added and heated at 70° under vigorous stirring. heating was continued until no starting material was detected in the TLC test (solvent system III). The cooled reaction system was acidified carefully with aqueous alcoholic hydrochloric acid. The aqueous organic reaction mixture was amply diluted with water, the oily fraction separated was extracted with chloroform. The chloroform phase was washed until neutral, dried and evaporated to dryness. The crystalline oily residue obtained was subjected to chromatographic separation using a mixture of chloroform and benzene (1:3). The pure substance obtained was crystallized from a mixture of chloroform and petroleum ether (Table 3).

16 - *Methylandrost* - 5 - *ene* - 3β,17 - *diol* - 3,17 - *diacetate* (**10c**, **11c**, **12c**, **13c**). *General method* 2. Compound **10a**, **11a**, **12a**, **13a** (0.01 g/mol) was dissolved in a mixture of pyridine (10 mL) and acetic anhydride (5 g, 0.005 g/mol) and allowed to stand for 24 h. It was then diluted with water, the crystalline precipitate was filtered off, washed and dried. The product was crystallized from a mixture of methanol and water (Table 3).

16 - *Methylandrost* - 5 - *ene* - 3β,17β - *diol* - 3 *acetate* (**11b**, **13b**). *General method* 3. Compounds **11a** and **13a** (0.01 g/mol) were dissolved in anhydrous pyridine (20 mL), then a solution of acetic anhydride (2 mL; 0.02 g/mol) in pyridine (10 mL) was added dropwise while cooling in ice and stirring continuously. The progress of the reactions were monitored by TLC. The reaction mixtures were poured into a mixture of sulphuric acid (10 mL) and ice (100 g) and extracted with benzene. The benzene phase evaporated to dryness and subjected to chromatographic separation. The monoacetates (**11b**, **13b**) were eluted in benzene-petroleum ether (3:1) (Table 3).

16 - *Methylandrost* - 5 - *ene* - 3β - *ol* - 17 - *one* 3 *acetate* (**2b**, **3b**). *General method* 4. Compounds **11b**, **13b** (0.01 g/mol) were dissolved in acetone (10 mL), cooled in ice and Jones' reagent (4 mL) was added to them. After 1 h, the reaction mixtures were diluted with water, the crystalline precipitates were filtered off, washed until neutral, then crystallized from a mixture of methanol and water (Table 3).

Micro hydrogenation of **1b** *in the presence of Pd–C* (**21**). In a microhydrogenating apparatus of Bretschneider-Burger type, Pd–C (25 mg) was suspended in ethanol (2 mL) under H_2 for 180 min. **1b** (0.043; 0.1 mmol) was added to the reaction mixture. Absorption of one equivalent of H_2 took place in 15 min. The catalyst was filtered off from the reaction mixture, the alcoholic solution was diluted with water and the crystals were filtered off. **3b**: 0.0295 g (86.2%) (Table 3).

Micro hydrogenation of **1b** *in the presence of Raney nickel.* Compound **1b** (0.034 g 0.0 mmole) was hydrogenated in the presence of Raney Ni (25 mg). The reaction mixture consumed 2 equivalents of H_2 in 180 min. **13b**: 0.0285 g (83.3%) (Table 3).

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