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EPIMERIZATION AT A QUATERNARY C-SUBSTITUTED CARBON ATOM

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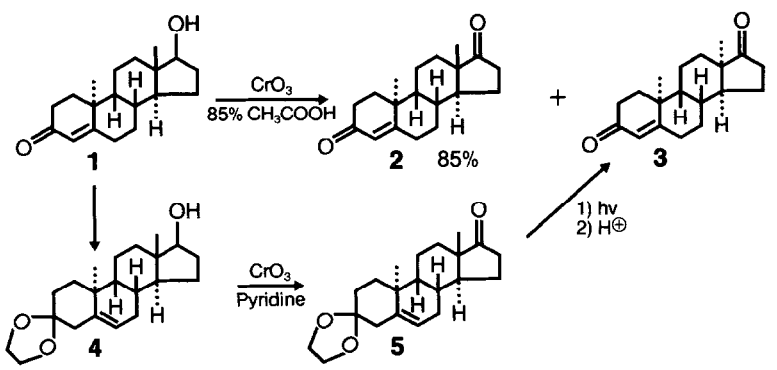
Abstract—Oxidation of secondary alcohols of different structures with chromic acid in aqueous acetic acid or chromic anhydride in acetic anhydride has been found to be accompanied by partial epimerization at the adjacent quaternary C-atom. In the case of compound **24**, this epimerization amounts to 45%. Reaction conditions and the structure of the alcohol influencing the extent of epimerization have been investigated. With compound **10** it has been proved that epimerization occurs prior to oxidation to the ketone. A possible reaction mechanism is discussed.

Some years ago we reported that chromic acid oxidation of the 17β-OH group of 9β,10α-testosterone led not only to the expected 9β,10α-androstenedione, but also in part to its C(13)-epimer.[a,b] At that time only the photolytic epimerisation at C(13) of 17-ketones was known. In the mean-time, epimerization at C(13) has also been observed under other conditions. Kirk *et al.*[1] and Hirschmann *et al.*[2] have reported on inversion of configuration at C(13) of D-homo-steroids by solvolysis of 17β-tosylates. Jacquesy[3] has obtained 13α-steroids by treatment of pregnane-20-ketones with hyperacids such as HF/SbF_5 or HSO_3F/SbF_3. Finally, Barton *et al.*[4] observed epimerization at C(13) by refluxing a 17-hydroxyimino-steroid in acetic anhydride and pyridine. We have investigated further our original observation and examined the course of the reaction with a series of structurally different compounds.

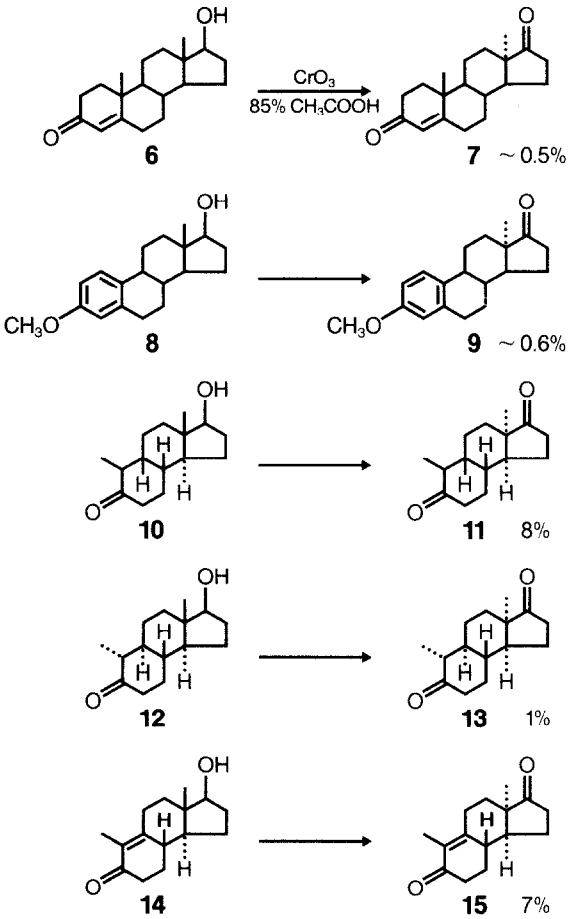
Oxidizing 9β,10α-testosterone (retrotestosterone) **1** with chromic acid in 85% aqueous acetic acid, we obtained the expected 17-ketone **2** in 85% yield. As an unexpected by-product of this oxidation 6–8% of an isomeric ketone was formed. The fact that the ORD-curve of this isomeric ketone exhibited an inverse Cotton effect compared to **2**, and that in the ^{1}H-NMR-spectrum of this compound the signal of the 18-Me group was shifted downfield by 0.11 ppm, indicated that epimerization at C(13) must have taken place. This was proved as follows: 9β,10α-testosterone **1** was transformed via **4** by oxidation with chromic anhydride in pyridine to **5**. Irradiation of **5** with a high pressure mercury lamp in ether solution, subsequent removal of the protecting group, isomerization and chromatography led to a preparation which was identical with the above by-product. Inversion of the 13-Me group by irradiation of 17-keto-steroids has



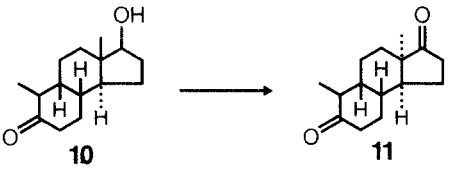
Scheme 1.

[a]5th International Symposium on the Chemistry of Natural Products, London, 8–13 July 1968, Abstracts F47, p. 354.

[b]This report is dedicated to the memory of the late Professor R. B. Woodward, who showed marked interest in our original observation communicated to him in 1968.[9]



Scheme 2. Extent of isomerization (vpc determination[c]) in %.



reaction conditions CrO_3 in[4]	% inversion (vpc analysis)
85% CH_3COOH	6–8
8N H_2SO_4 acetone, 0°	0
Pyridine	0
Dimethylformamide	0
Acetic anhydride	15

Scheme 3.

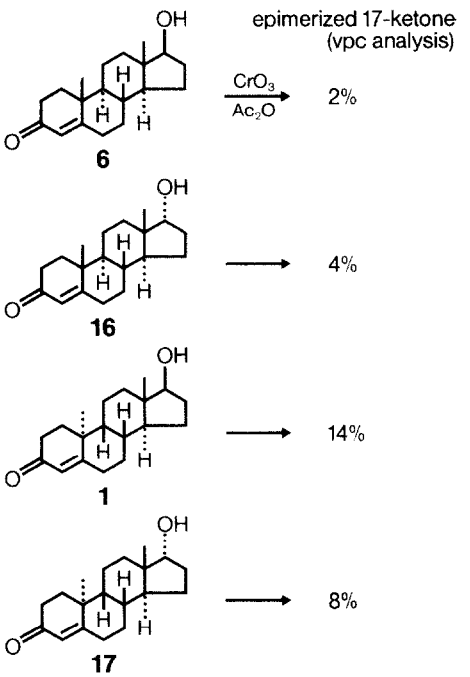
been found by Butenandt.[5] Bots[6] has used this method to synthesize 13α-androst-4-ene-3,17-dione.

To our knowledge such an isomerization with chromic acid oxidation of a secondary alcohol has not been reported before. We therefore investigated the reaction with various tetracyclic and tricyclic compounds having the same relative position of the quaternary C-atom and the secondary OH-group as in **1**. Using exactly the same conditions (Experimental, standard procedure 1) the yield of the epimeric ketone was drastically influenced by the stereochemical and structural changes of the starting material (Scheme 2).

The influence of solvent systems frequently used for chromic acid oxidations has been tested next. Since compound **11** and its C(13)-isomer were suitable for vpc-analysis, their parent alcohol **10** has been used as starting material. Results are summarized in Scheme 3.

As acetic anhydride appeared to favour the epimerization, in the following experiments the oxidations were all carried out in this solvent.

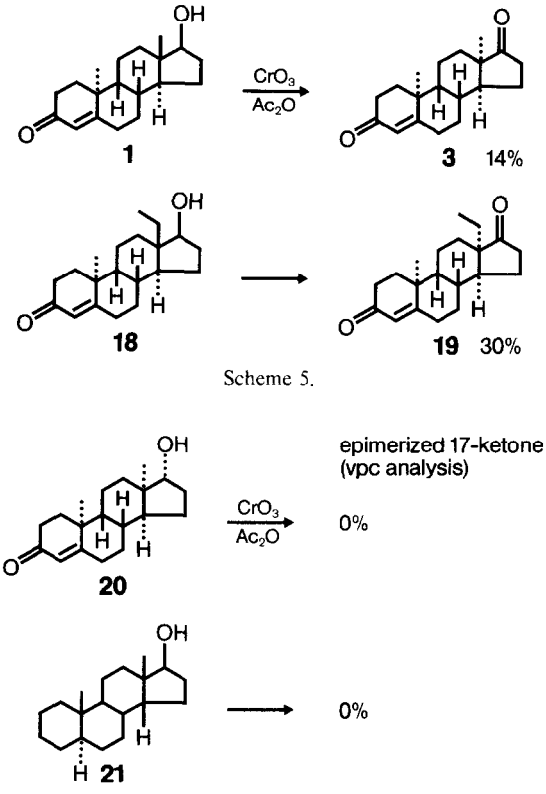
The relative configuration of the angular Me group and the OH group exerts an influence on the extent of epimerization; however, it seems to operate in different directions in the two pairs of compounds examined (Scheme 4). The nature of the angular C(13)-alkyl group markedly influenced the degree of epimerization (Scheme 5). Furthermore it is interesting to note that the tetracyclic compounds **20** and **21**[7] with C/D-*cis* configuration did not show any epimerization (Scheme 6). Finally we have investigated two pairs of racemic hydrindane alcohols. From the following results (Scheme 7) it can be concluded that in these cases the conversion of the *trans*-derivatives to the *cis*-series is favored, to the extent in one case that nearly half of the



Scheme 4.

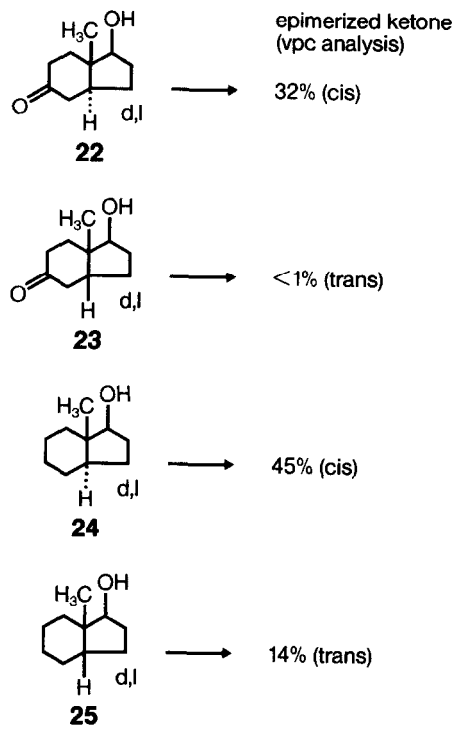
[c]With these oxidations small amounts of acidic products were always formed. For the vpc-determination only the neutral fraction was used and the percentages refer to the ratio of the abnormal and normal ketones. Retention times were compared with authentic samples.

[d]Reactions were run with excess of CrO_3 at room temperature until no more starting material could be detected by tlc.



Scheme 5.

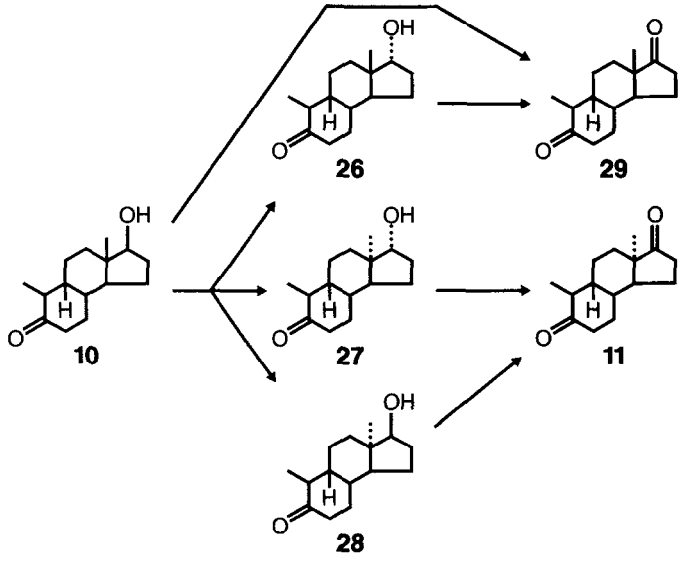
Scheme 6.



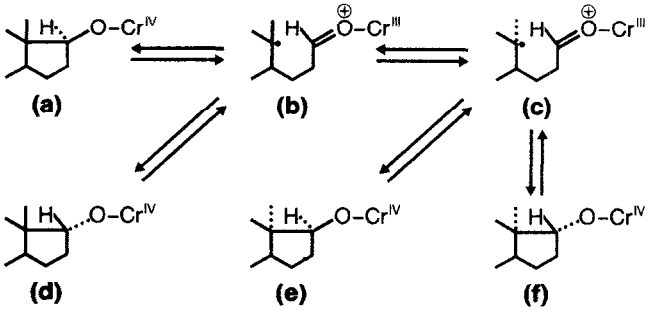
Scheme 7.

ketone obtained was epimerized. In order to elucidate the epimerization reaction, some further investigations have been made. The following has been found: (1) The epimerization is completely suppressed in the presence of manganous perchlorate while the normal oxidation to the 17-ketone is not influenced. This indicates that Cr^{IV} of Cr^{V} must be involved in the epimerization, since manganous ions reduce these chromium species very rapidly and therefore act as Cr^{IV}- or Cr^{V}-scavengers.[8] (2) The simultaneous oxidation of compound **10** and an excess of a secondary alcohol as e.g. isopropanol leads to a higher extent of epimerization. A possible explanation for this finding is that by the simultaneous oxidation of another alcohol more Cr^{IV} and/or Cr^{V} is generated. (3) Both C(13)-epimeric ketones are completely stable under the reaction conditions. (4) The extent of epimerization is unchanged when the oxidation is run in the dark, which proves that light is not involved.

The fact that epimerization has occurred before oxidation, has been proved by the following experiment: Compound **10** was oxidized in presence of



Scheme 8.



Scheme 9.

isopropanol and the reaction was stopped when about half of **10** had been oxidized to the ketone. The recovered alcoholic fraction consisted of 4 compounds in a ratio of 89:5:5:1 (vpc analysis). By careful chromatography we have been able to isolate and identify compounds as **10**, **26**, **27**. The presence of **28** could be postulated from NMR and MS data. The following scheme represents a possible mechanism of this epimerization involving a Cr^{IV}- or Cr^{V}-ester in equilibration with 2 possible oxonium radicals which are in their turn in an equilibrium with the isomerized ring-closed compounds. This mechanism, which we proposed in our preliminary report,[a] is similar to that proposed by Barton for the epimerization of 17-hydroxyimino-steroids,[4] but is different from the other observed epimerizations.[1-3]

In conclusion we would like to stress, that one has to take into account that oxidations of secondary alcohols with chromic anhydride in acetic acid or acetic anhydride can lead to epimerized products.

EXPERIMENTAL

For column chromatography Silicagel of 0.06–0.2 mesh (Merck) was used. Tlc on Merck-plates, Silicagel F254; identification by spraying with 50% *p*-toluenesulfonic acid. All m.ps are uncorrected. $[\alpha]_D$-values were taken from the ORD spectra, which have been measured in 0.1% dioxane soln (max = maximum; min = minimum). UV spectra were measured in optically pure EtOH on a Cary 14, λ_{max}-values are indicated in nm, ε-values in parenthesis. IR spectra in KBr on a Beckman IR 9 (only typical and intensive bands (in cm^{-1}) are reported). ^{1}H-NMR spectra have been measured in $CDCl_3$ on a Varian A 60, chemical shifts are in ppm relative to internal TMS; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, J = coupling constant in c/s. MS spectra have been recorded on a MS 9 (AEI, Manchester), after the mass numbers, peak intensities are given in % relative to the highest peak.

1. *Oxidation with* CrO_3 *in 85% aqueous acetic acid*

Standard procedure. To 4 mmoles of the secondary alcohol in 10 ml 85% aqueous AcOH was added a soln of 400 mg of CrO_3 in 10 ml 85% AcOH. The mixture was stirred for 3 hr at room temp. 1 ml MeOH was added, the mixture stirred for 10 more min, then it was poured on ice-water and extracted with ether. The ether extract was washed twice with 5% NaOHaq, then with water until neutral and finally it was dried with Na_2SO_4 and evaporated to dryness. The crude product was analyzed by vpc comparison with authentic samples, where possible. New products were fully characterized by IR, NMR, MS and ORD spectra.

2. *Oxidation with* CrO_3 *in acetic anhydride*

Standard procedure. To 4 mmoles of the secondary alcohol dissolved in 10 ml Ac_2O a soln of 400 mg CrO_3 in 10 ml Ac_2O was added with stirring during 30 min at room temp. The mixture was then stirred for another hr. The mixture was worked up as under (1) and the crude product was analysed by vpc.

The following new compounds were isolated and characterized:

9β,10α,13α-androst-4-ene-3,17-dione (**3**). The crude oxidation product was chromatographed on aluminium oxide (act. II) with benzene-hexane (1:1). The first fractions containing pure 3 (tlc) were combined and recrystallized from dichloromethane-isopropyl ether. M.p. 90–91°. $[\alpha]_D = -176°$. ORD: $\alpha_{(302)} = -840°$ (min), $\alpha_{(306)} = -800°$ (max), $\alpha_{(312)} = -960°$ (min), $\alpha_{(326)} = -830°$ (min), $\alpha_{(335)} = -430°$ (max), $\alpha_{(342)} = -720°$ (min), $\alpha_{(348)} = -550°$ (max), $\alpha_{(355)} = -1053°$ (min), $\alpha_{(365)} = -898°$ (max), $\alpha_{(374)} = -1075°$ (min). UV: 240 (16300). IR: 2920, 2890, 2830, 1731, 1664, 1609, 1450, 1265, 1230, 1180. ^{1}H-NMR: 1.14 (s, CH_3-C(13)), 1.28 (s, CH_3-C(10)), 5.77 (s, H-C(4)). MS: 286 (16, M), 271 (3), 244 (9), 163 (19), 162 (13), 150 (33), 124 (100), 107 (34), 97 (43), 79 (32). (Found: C 79.47; H, 9.05. $C_{19}H_{26}O_2$ (286.40) Calc. for C, 79.68; H, 9.15%).

Synthesis of compound **3** *from 3,3-ethylenedioxy-9β,10α-androst-5-en-17-one* (**5**). A soln of 2.0 g **5** in 200 ml ether was irradiated at 16° with a mercury high pressure lamp for 3 hr. The soln was evaporated to dryness, the residue dissolved in a soln of 2 g *p*-toluenesulfonic acid in 50 ml EtOH and 5 ml water. The mixture was kept 4 hr at 25°, poured on ice-water and extracted with ether. The ether-extract yielded after washing with water and drying with Na_2SO_4 1.95 g crude product, which was chromatographed on aluminium oxide (act. II). By tlc uniform fractions were combined and recrystallized from ether-hexane. The product obtained, m.p. 90°, was identical with the compound isolated above.

Des-A-9β,13α-androstane-5,17-dione (**11**). The crude oxidation product from **10** was chromatographed on Silicagel with ether-cyclohexane (1:1). The first fractions contained pure **11**. Recrystallized from ether-hexane, it melted at 105–106°. $[\alpha]_D = -96°$. ORD: $\alpha_{(230)} = 1820°$, $\alpha_{(280)} = -1030°$, $\alpha_{(305)} = +600°$ (max), $\alpha_{(325)} = -600°$ (min), $\alpha_{(380)} = -246°$. IR: 2950, 2880, 1725, 1702, 1458, 1410, 1375, 1090, 1015. ^{1}H-NMR: 1.03 (d, J = 6.3, CH_3-C(10)), 1.10 (s, CH_3-C(13)). MS: 234 (21, M), 219 (6), 216 (9), 190 (16), 162 (85), 136 (39), 121 (56), 110 (61), 97 (95), 55 (86), 41 (100). (Found: C, 76.85; H, 9.34. Calc. for $C_{15}H_{22}O_2$ (234.35) C, 76.88; H, 9.46%).

Synthesis of compound **11** *from 5,5-ethylenedioxy-des-A-9β-androstan-17-one.* By irradiation of 5,5-ethylenedioxy-des-A-9β-androstan-17-one[15] as described for **3**, compound **11** was isolated in about 15% yield.

Des-A-13α-androst-9-en-5,17-dione (**15**). The crude oxidation product from **14** was chromatographed twice on Silicagel with ether–hexane (1:1). The first fractions contained **15**. The tlc-pure fractions were combined and recrystallized from acetone-hexane. m.p. 115–116°. $[\alpha]_D = -126°$. ORD: $\alpha_{(250)} = -2500°$, $\alpha_{(265)} = +2000°$ (max), $\alpha_{(313)} = -2020°$ (min), $\alpha_{(318)} = -1830°$ (max), $\alpha_{(324)} = -2330°$ (min), $\alpha_{(370)} = -602°$. UV: 249 (15500). IR: 2900, 2860, 1732, 1651, 1628, 1444, 1205, 1138, 1080. ^{1}H-NMR: 1.06 (s, CH_3–C(13)), 1.81 (d, J = 2.5, CH_3–C(10)). MS: 232 (15, M), 175 (10), 161 (8), 136 (100), 119 (15), 105 (19), 97 (91). (Found: C, 77.17; H, 8.62. Calc. for $C_{15}H_{20}O_2$ (232.33): C, 77.55; H, 8.68%).

The same compound was obtained by irradiation of 5,5-ethylenedioxy-des-A-androst-9-(11)-en-17-one, acid hydrolysis and chromatography on Silicagel (as described for **3**) in about 30% yield.

9β,10α,17α-Testosterone (**17**).[e] This compound has been synthesized by acetolysis of 9β,10α-testosterone-*p*-toluenesufonate with KOAc in AcOH (18 hr reflux), chromatographic purification of the 17α-acetate and subsequent hydrolysis with K_2CO_3 in MeOH. m.p. 217–219°, $[\alpha]_D = +66°$. UV: 241 (16400).

9β,10α,13α,17α-Testosterone (**20**). To a soln of **3** in 100 ml MeOH was added a soln of 3 g $NaBH_4$ in 160 ml MeOH and 20 ml water. The mixture was stirred for 2 hr, then poured on ice–water and extracted with CH_2Cl_2. The organic extract was washed with water, dried with Na_2SO_4 and evaporated to dryness. The residue was dissolved in 100 ml of $CHCl_3$ and stirred for 2 hr with 15 g of MnO_2. The mixture was filtered and evaporated to dryness. The residue was recrystallized twice from ether to give 1.9 g pure **20**. M.p. 116—118°. $[\alpha]_D = -70°$. ORD: $\alpha_{(270)} = +1080°$, $\alpha_{(290)} = +830°$, $\alpha_{(320)} = +1190°$ (max), $\alpha_{(284)} = +770°$ (min), $\alpha_{(357)} = -1002°$ (min), $\alpha_{(364)} = -822°$ (max), $\alpha_{(373)} = -1100°$ (min). UV: 242 (15900). IR: 3400, 2920, 2840, 1655, 1620, 1460, 1442, 1315, 1230, 1107, 1080. ^{1}H-NMR: 1.08 (s, CH_3–C(13)), 1.23 (s, CH_3–C(10)), 3.78 (m, H–C(17)), 5.76 (d, J = 1.5, H–C(4)). (Found: C, 79.29; H, 9.85. Calc. for $C_{19}H_{28}O_2$ (288.41): C, 79.12; H, 9.79%).

Isolation of 17α-hydroxy-des-A-9β-androstan-5-one (**26**) *and 17α-hydroxy-des-A-9β,13α-androstan-5-one* (**27**). To a soln of 30 g of **10** and 3.8 ml isopropanol in 170 ml Ac_2O was added within 45 min a soln of 6.4 g CrO_3 in 120 ml Ac_2O. The mixture was stirred for another 30 min and then worked up as described in the standard procedure. The crude oxidation product was chromatographed on 3 kg Silicagel. With CH_2Cl_2–Me_2CO (96:4) 17.2 g of a mixture of **11** and **29** were eluated. The CH_2Cl_2–Me_2CO (9:1 and 4:1) eluates yielded 9.5 g of an alcoholic fraction which consisted by VPC–MS-analysis of four isomeric compounds (mass 236) in a ratio of 89:5:5:1. This mixture was rechromatographed with CH_2Cl_2. The first fractions yielded pure **27**, m.p. 124–125° (ether–hexane). $[\alpha]_D = -50°$. ORD: $\alpha_{(230)} = -1461°$, $\alpha_{(267)} = -1787°$ (min), $\alpha_{(312)} = +886°$ (max), $\alpha_{(362)} = 0°$. IR: 3510, 2920, 1703, 1658, 1410, 1373, 1122, 1077, 1030. ^{1}H-NMR: 1.01 (s, CH_3–C(13)), 1.03 (d, J = 6.5, CH_3–C(10)), 4.16 (~tr, J = 7, H–C(17)). MS: 236 (20, M), 218 (26), 177 (36), 161 (24), 135 (25), 124 (44), 108 (71), 95 (51), 81 (55), 67 (55), 55 (90), 41 (100). (Found: C, 76.08; H, 10.15. Calc. for $C_{15}H_{24}O_2$ (236.37): C, 76.22; H, 10.24%).

The further eluates yielded mixtures of **10** and **27**; then the following fractions gave 5.8 g of pure **10**. Finally the CH_2Cl_2–Me_2CO (1:1) eluates yielded pure **26**, m.p. 69–70° (ether–hexane). $[\alpha]_D = -49°$. ORD: $\alpha_{(230)} = -1105°$, $\alpha_{(264)} = -1205°$ (min), $\alpha_{(313)} = +436°$ (max), $\alpha_{(436)} = -73°$. IR: 3624, 2960, 1709, 1455, 1380, 1040. ^{1}H-NMR: 0.77 (s, CH_3–C(13)), 1.03 (d, J = 6.5, CH_3–C(10)), 3.85 (d, J = 5.6, H–C(17)). MS: 236 (47, M), 218 (16), 81 (55), 55 (91), 41 (100). (Found: C, 76.33; H, 10.17%. Calc. for $C_{15}H_{24}O_2$ (236.37): C, 76.23; H, 10.24%).

The fourth isomer presumed to be **28** could not be isolated from the chromatogram.

Compound **26** gave by Jones-oxidation the dione **29**, and oxidation of **27** yielded **11**.

Compound **27** was also obtained by $NaBH_4$-reduction of the 5-ketal of **11** and subsequent acid hydrolysis. The following compounds necessary as starting materials or for vpc comparisons were synthesized according to the indicated literature: Compound **7**[6,f] **9**,[9] **1**,[10] **2**,[10] **16**,[11] **18**,[12,f] **19**,[12,f] **21**,[7,g] **22**,[13,h] **23**,[13,h] **24**,[14] **25**,[14] **10** and des-A-9β-androstane-5,17-dione:[15] **12** and des-A-10α-androstane-5,17-dione:[16] **14** and des-A-androst-9-ene-5,17-dione.[17]

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[e]We thank Dr. P. Keller, Pharm. Research Dept., F. Hoffmann-La Roche & Cie Ltd., Basel, for synthesizing this compound.

[f]This compound has been obtained from Mr. P. Westerhof, Philips-Duphar, Weesp, Holland.

[g]We thank Prof. Y. Mazur, The Weizmann Institute of Science, Rehovoth, Israel, for making available this substance.

[h]Compound **22** and **23** and the corresponding diones have been obtained from Dr. Z. Hajos, Chem. Res. Dept., Hoffmann-La Roche Inc., Nutley, N.J., USA.

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