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SOME REARRANGEMENTS INITIATED BY METHYLENE TRIPHENYLPHOSPHORANE

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Abstract—Treatment of 17α-acetyl-Δ⁵-estren-17β-ol with methylene triphenylphosphorane initiates a D-homo rearrangement followed by the intended Wittig reaction. This rearrangement can be explained by the proton abstracting properties of the applied Wittig reagent. These properties are also responsible for the rearrangements observed when using 17α-acetyl-Δ⁵-estren-17β-ol 17-acetate as a substrate. They lead to an intramolecular condensation of the acetyl- and acetoxy-side-chain. Subsequent reactions depend on the conditions used

The nucleophilic character of methylene triphenylphosphorane—a widely used Witting reagent†—has often been brought forward to explain observed enolisations under conditions normally applied for Wittig reactions, but rarely to substantiate other types of rearrangements.[1]

Some rearrangements are presented of α-ketols and α-keto acetates initiated by molecular characteristics of the methylene triphenylphosphorane reagent.

Rearrangement of the α-ketol (**1**). A Wittig reaction with methylene triphenylphosphorane on the α-ketol **1** (Fig. 1) in a mixture of DMSO and THF gave two epimeric D-homo compounds (**4a,b**) in a ratio of 65:35. No trace of the expected 20-methylene-derivative **5** or the isomeric D-homo compounds **6a,b** could be detected. Structure elucidation of the D-homo compounds **4a,b** is based on spectral data: in both compounds NMR signals (60 and 90 MHz) are observed characteristic for an exocyclic methylene group. These data do not completely rule out the structures **6a,b**; so for a conclusive proof of structure of the reaction products we repeated the reaction sequence starting with **3**, and subjected the D-homo compounds **7a,b** to ozonization and subsequent reduction with LAH (Fig. 1).

Ozonization of compound **7a,b** yielded as main reaction product an unidentified acid which could be reduced with LAH to the corresponding diol **8**; as a minor reaction product (7%) the ozonization yielded the D-homo ketone **10**; its structure could unambiguously be proven by IR and NMR data.[1]

The isolation of the D-homo ketone **10** is already a proof of structure for compound **7a,b**, but moreover the obtained diol **8** can clearly be distinguished from the diol **9** that should originate from the alternative reaction product, compound **6a,b**. The protons at C_{17} and C_{17a} of the diol **9** should give a multiplet and a singlet respectively, in the NMR spectrum, whereas those of the diol **8** should give a triplet and a quartet respectively, which was actually observed.

The course of the D-homo rearrangement can be explained in two ways: proton abstraction from the OH group, or intermediate complexation of the phosphor of the Witting reagent with the carbonyl-oxygen of the side-chain.

Abstraction of the OH proton may initiate an acyloin-like rearrangement to give rise to the formation of the D-homo ketones **1c** which may act as substrate for the phosphorane reagent to yield the D-homo compounds **4a,b** (Fig. 2, route A).

An originally formed phosphor-oxygen complex, on the other hand, may result in an increased electron deficiency on the carbonyl-carbon which in turn may initiate a rearrangement following the same lines as mentioned before (Fig. 2, route B).[2]

Performance of the reaction with short measure of the phosphorane reagent—mole ratio ratio 9:10—resulted in the formation of the epimeric D-homo ketones **11a,b** (yield: 15% and 15% resp) next to the epimeric D-homo methylene compounds **4a,b** (yield: 30% and 30% resp). Hardly any starting material was detectable. The structures of compounds **11a, b** were unambiguously proven by IR and NMR data.[1]

The available data do not give enough conclusive evidence to favour one of the pathways over the other (Fig. 2). Isolation of the D-homo compounds **11a,b** makes it only reasonable that the intermediate **1c** is involved.

The isolation of the D-homo ketones **11a,b** confirms, moreover, the assumption that the Wittig reaction is preceded by the D-homo rearrangement. Remarkably this rearrangement does not go in a stereospecific manner as generally is observed.[2]

The complexated phosphorane reagent may be responsible for this anomalous behaviour. A Witting reaction on the pure D-homo ketone **11a** surprisingly resulted also in an epimeric mixture of the D-homo compounds **4a,b**.

The originally wanted isopropenyl compound **5** could be obtained—in yields not exceeding 25%—by carrying out the Wittig reaction (in toluene/pyridine) on the silylether **2**. Changing from toluene/pyridine to DMSO as a solvent gave again compounds **4a,b** as the main reaction products.

A direct explanation for this solvent effect can not be given yet, although the difference in polarity of the applied solvents might indicate that under polar conditions (DMSO) the oxygen–silicium bond is weaker than in a more polar medium.

Dissociation of this oxygen–silicium bond generates the intermediate **1a** (Fig. 2) which subsequently rearranges further via the intermediate **1c** to the D-homo methylene compounds **4a,b**.

Rearrangements of the α-keto acetate (**12**). Unexpected results were also obtained when it was tried to protect the 17β-OH group as the acetate. Under relatively apolar

† All Wittig reactions carried out were checked for the absence of the base (sodium hydride, dimsyl sodium, butyllithium, etc.) applied to generate the phosphorane reagent.

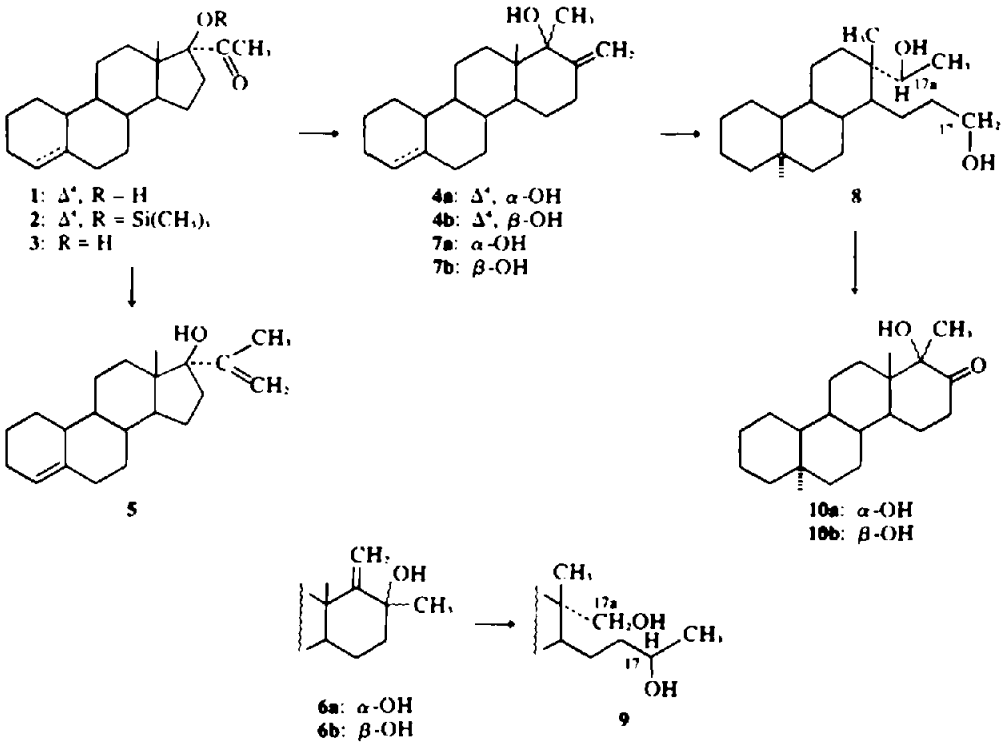


Fig. 1.

conditions—using toluene as a solvent—the phosphorane reagent reacts with the substrate to yield the diketone **13** (60%) as the main reaction product. In more polar solvents like DMSO, THF and t-butanol the two spiro-compounds **14** and **15** are formed instead (yield: 30% and 60% resp).

These two spiro-compounds are also isolated when instead of the phosphorane reagent one of the following bases is used: potassium-t-butoxide (in t-butanol), or sodiumhydride (in DMSO).

Structure elucidations of the diketone **13** and the spiro-lactone **15** are based on spectral data (IR, NMR, UV and Mass); the structure proposals for these two compounds are strongly supported by reference data of compounds containing similar structure moieties.[4a]

Spectral data did not completely define the proposed structure of the spiro-compound **14** in leaving open the possibility of the presence of a spiro-ether (as shown in **14**) or a spiro-lactone (like compound **16**).

Some examples of similar spiro-lactones are known

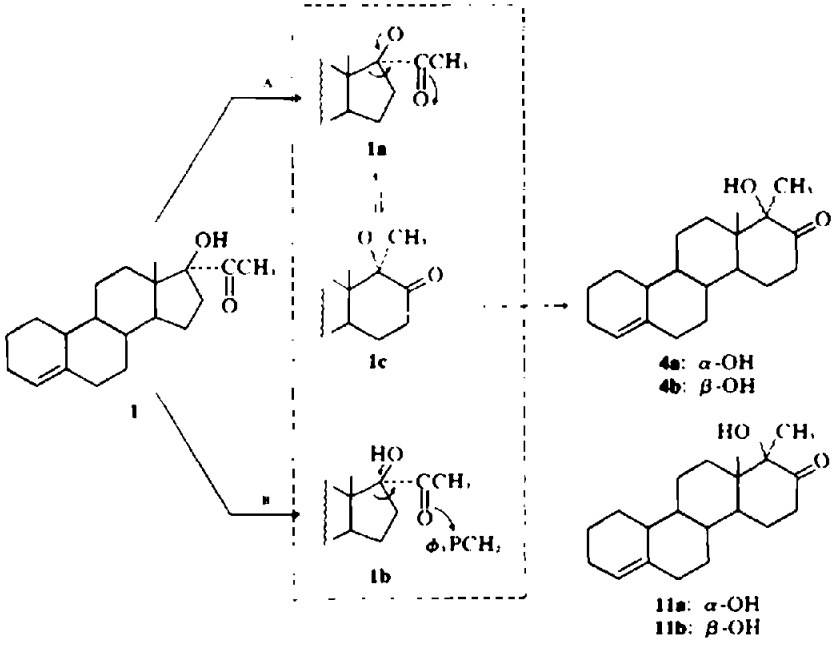


Fig. 2.

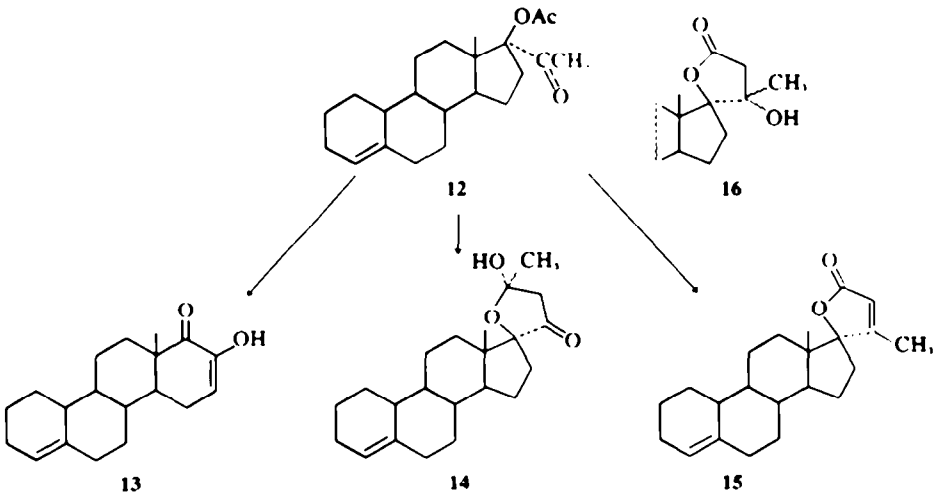


Fig. 3.

from literature, in particular from a publication by Lehmann, who performed some experiments quite similar to the ones described here; the only difference being the substrate and the applied base (NaOH/DMSO).[1] The spectral data favour the structures containing a spiro-ether over those with a spiro-lactone, not ruling out the latter ones completely, however (compare Table 1, see p. 1545).

The reaction products strongly indicate that under certain Wittig conditions—DMSO, THF, t-butanol—proton-abstraction occurs both from the acetyl- and from the acetoxy-group leading to the corresponding spiro-ether **14** and the spiro-lactone **15**. For unknown reasons the spiro-ether **14** is stable under the reaction conditions, whereas the intermediate **16** dehydrates to the unsaturated lactone **15** (Fig. 4).

The formation of the diketone **13** on the other hand, can be rationalised by assuming that the intermediate spiro-ether, being unstable in the applied apolar medium, will rearrange further to a D-homo intermediate, which in turn after a retro-aldol condensation will yield the diketone **13**. This mechanism is substantiated by the observation that, according to TLC, in the course of the reaction (in apolar medium) an intermediate product has been formed, which in course of time disappears under simultaneous formation of the diketone **13**. That the anion **12b** was the intermediate was proven by quenching the reaction mixture and isolation and identification of the spiro-ether **14**.

In order to support the correct structure of the spiro-compounds, a series of experiments was performed in which the substrate **12** (17α-acetyl, 17β-acetoxy)

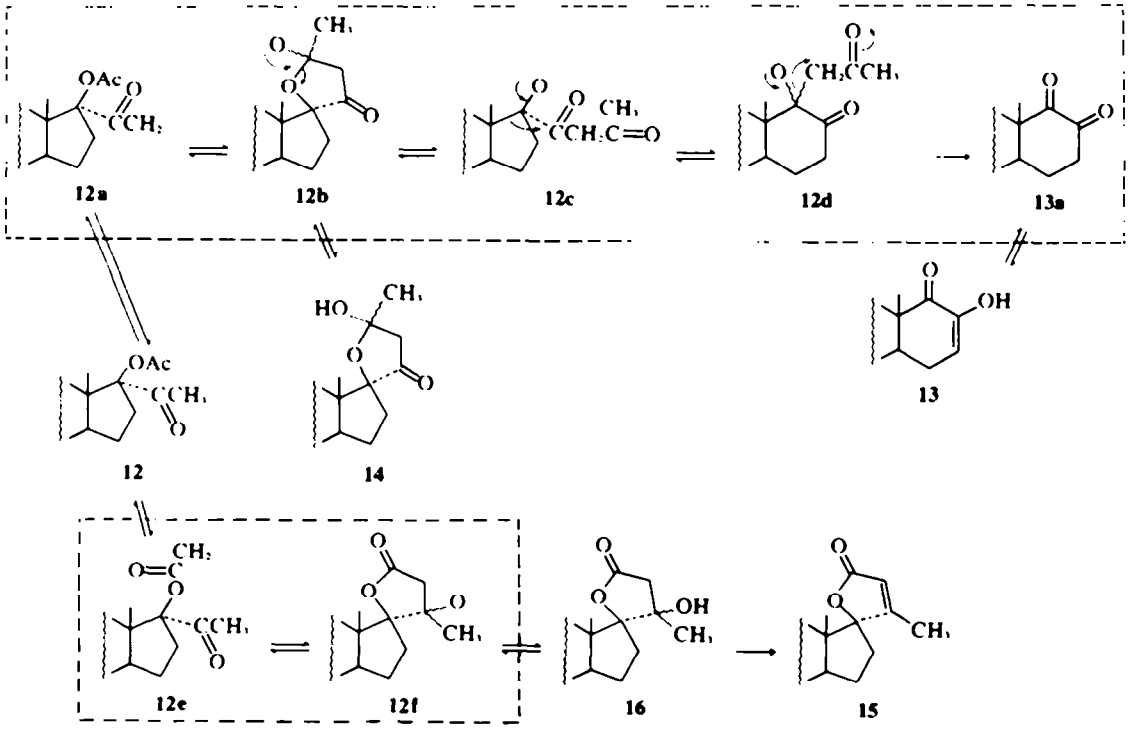


Fig. 4.

as well as "Lehmanns" substrate **17** (17α-acetoxy, 17β-acetyl) were treated under several alkaline conditions, as summarized in Fig. 5. All reactions studied were carried out in DMSO, to exclude a possible solvent effect.

Figure 5 illustrates the observation that:

(1) Under all alkaline conditions applied the α-acetoxy-compound **17** is converted into a spiro-lactone structure (**19** and **20**).

(2) With sodium hydroxide compound **12** also rearranges to a spiro-lactone (**16**) as main reaction product; but under Wittig conditions and when applying dimsyl-sodium as a base the formation of the spiro-lactone **15** is accompanied by that of the spiro-ether **14**.

Obviously proton abstraction from the acetyl-group is in most cases responsible for the ultimate course of the reaction. Only in the conversion of compound **12** a competition in proton abstraction from the acetyl- and acetoxy-group, respectively, can under some conditions be observed. Apparently the position of the side-chain does have some influence on the course of the reaction.

The pronounced influence of the solvent used is dramatically shown when turning from DMSO to an aprotic solvent like toluene;

(1) Starting with compound **12** the diketone **13** (Fig. 3) is isolated as the only detectable reaction product under Wittig conditions, whereas in DMSO under the same conditions the spiro-compounds **14** and **15** could be detected.

(2) Starting with compound **17** surprisingly the spiro-ether **18** (Table 1) is formed under Wittig conditions, whereas in DMSO under the same conditions the spiro-lactone **19** is isolated.

The explanation for the discrepancy in reaction behaviour of the compounds **12** and **17** under Wittig conditions may be found in a difference in the position of the side-chains to each other in the two compounds.

Illustrative for the great similarity of the different spiro-compounds are their IR and NMR data. In the case of the saturated spiro-compounds only IR gives some direct information on the presence of either an ether or a lactone moiety. NMR adds no substantial evidence to the structure elucidation (ether versus lactone). For the unsaturated spiro-compounds even IR does not give conclusive evidence on the presence of an ether or lactone ring. Characteristic for all saturated spiro-compounds is the coupling constant found in NMR for the two ring protons (Table 1).

In view of the large spectral similarity of the different spiro-compounds a decisive experiment has been performed in which as well as the spiro-ether **18** as the spiro-lactone **19** were treated with the same base ($NaOH/CH_3OH$).†

Under these alkaline conditions the spiro-lactone dehydrated to its unsaturated analogue. Treatment of the corresponding spiro-ether, however, resulted in the formation of the D-homo compound **21** (Fig. 6). Structure elucidation of this latter compound is based on IR and NMR.

The alternative structure **22** could be excluded as no proton-coupling has been found between the olefinic side-chain proton and the C_{16}-methylene protons. A double resonance experiment revealed furthermore that a small coupling exists between the olefinic proton and the Me group next to the CO group ($J \sim 0.5$ Hz).[6]

Hardly any shift was observed for the olefinic side-chain proton in structure **21** when turning from a magnetic isotropic to a magnetic anisotropic solvent

†This part of the investigation has been carried out by Mr. J. G. C. M. Vermeer.

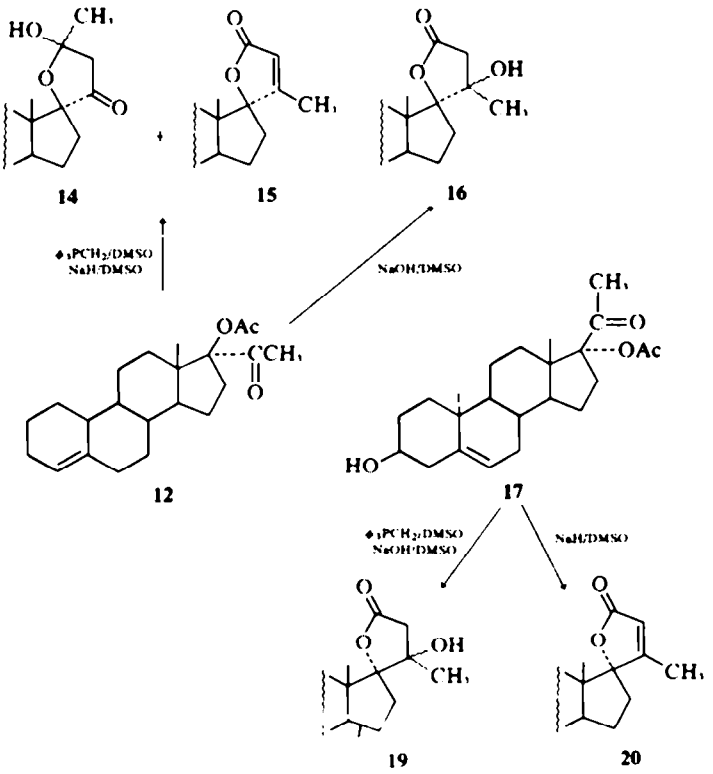
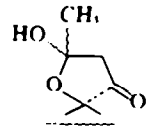


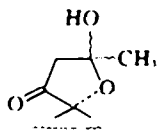
Fig. 5.

Table 1. IR and NMR data of the different spiro-ethers and spiro-lactones



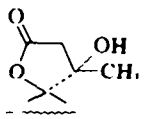
14

1752 cm $^{-1}$ (C=O)
1.62 ppm (CH_3)
0.92 ppm (18-CH_3)
2.52 ppm (2H's)
J_{AB} = −17 Hz



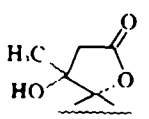
18

1750 cm $^{-1}$ (C=O)
1.67 ppm (CH_3)
0.80 ppm (18-CH_3)
2.47 ppm (2H's)
J_{AB} = −17 Hz



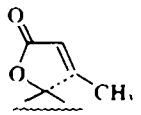
16

1774 cm $^{-1}$ (C=O)
1.51 ppm (CH_3)
1.00 ppm (18-CH_3)
2.63 ppm (2H's)
J_{AB} = −17 Hz



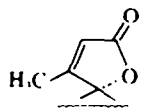
19

1775 cm $^{-1}$ (C=O)
1.54 ppm (CH_3)
0.97 ppm (18-CH_3)
2.61 ppm (2H's)
J_{AB} = −17 Hz



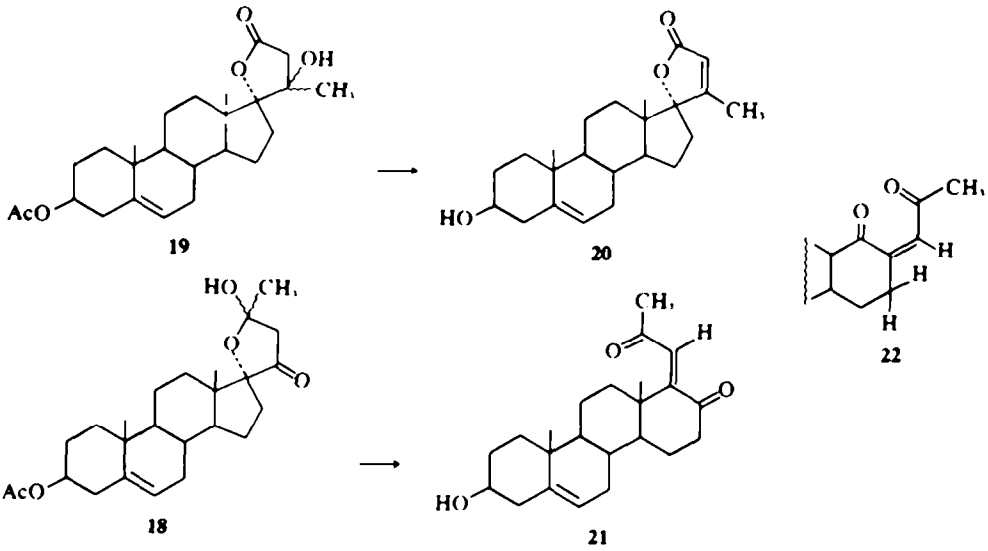
15

1742 cm $^{-1}$ (C=O)
2.30 ppm (CH_3; J = 1.5)
5.70 ppm (H; J = 1.5)
ϵ_{230} = 11.100



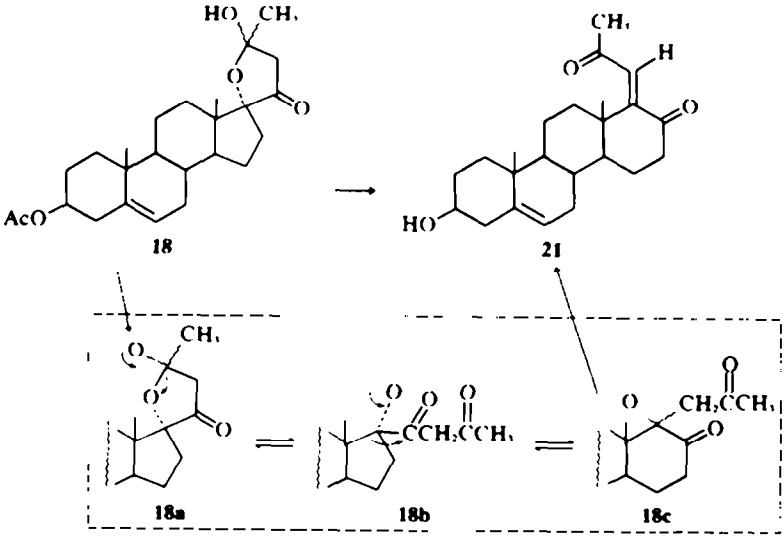
20

1743 cm $^{-1}$ (C=O)
2.17 ppm (CH_3; J = 0.6)
5.85 ppm (H; singlet)
ϵ_{230} = 11.100



19 **20** **22** **18** **21**

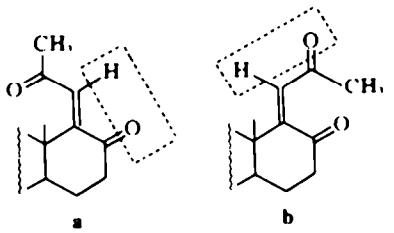
Fig. 6.



18 **21** **18a** **18b** **18c**

Fig. 7.

(deutero chloroform and benzene, resp). This observation indicates that the olefinic proton is situated in a plane through one of the two carbonyl C atoms perpendicular to the CO double bond leaving two structure alternatives: **a** and **b**. In view of the steric hindrance expected for the Me group and C_1–CO group in structure **b** (Dreiding models), slight preference exists for structure **a**.



a **b**

The isolation of the D-homo compound **21** shows unambiguously the presence of a spiro-ether moiety in the spiro-compounds **14** and **18**.

EXPERIMENTAL

M.ps were taken on a Büchi capillary apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter with concentrations of about 1% in $CHCl_3$ at 20°, unless otherwise stated. IR spectra (in cm^{-1}) were recorded in CCl_4, unless otherwise stated, on a Perkin-Elmer 357 spectrophotometer. NMR spectra were obtained with a Varian A-60D spectrometer in $CDCl_3$. Chemical shifts are reported relative to TMS as the internal standard.

A. *Preparation of starting materials*

17β - Hydroxy - Δ⁴ - 19 - nor - 17β - H - pregnen - 20 - one (**1**). Mercury(II) oxide (8.0 g) was suspended in a mixture of EtOH (200 ml) and water (140 ml), and conc H_2SO_4 (14.0 ml) was added. A slow stream of N_2 was passed over and the suspension was heated to 50°. A soln of *17α - ethinyl - Δ⁴ - estren - 17β - ol* (20.0 g) in a mixture of toluene (400 ml) and EtOH (200 ml) was added in 5 min. Stirring was continued for 0.5 hr at 55°. After cooling to room temp. the mixture was filtered through Hyflo, and the filtrate worked up (extraction). The residue (18.3 g) was crystallised from acetone, yield 15.5 g of **1** (m.p.: 165–167°). Analytical sample: m.p.: 169–170°; $[\alpha]_D$: +36°; IR (CH_2Cl_2): 1660, 801 (Δ⁴), 1701, 1688 (C=O), 3610 (OH); NMR: 5.40 (4-H), 2.24 (21-CH_3), 0.97 (18-CH_3). (Found: C, 79.2; H, 10.2. Calc. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; O, 10.58%). Chromatography of the mother liquor (3.0 g) on silicagel Merck G (30 parts) gave **11a** (0.45). Crystallisation was done from acetone/hexane; m.p. 167–169°; $[\alpha]_D$: −62°; IR (CH_2Cl_2): 1712 (C=O); 3598 (OH); NMR: 5.41 (4-H), 1.18 (17a-CH_3), 0.73 (18-CH_3).

17β - Hydroxy - Δ⁴ - 19 - nor - 17β - H - 20 - one 17β - trimethylsilylether (**2**). Compound **1** (20.0 g) was dissolved in dimethyl acetamide (200 ml)—dried before use over molecular sieves—and dry pyridine (24 ml). Chlorotrimethylsilane (24 ml) was added and the mixture was kept at room temp. for 3 hr, then poured into an ice-cold K_2CO_3 aq. The ppt was sucked off, washed with water and dried. The crude product was filtered through alumina (100 g) in n-hexane. The filtrate was concentrated to a small volume and kept for 3 hr at 0°. The crystals were sucked off and dried, yield: 20.0 g of **2**. From the mother liquor a second crop of 2.1 g was obtained. M.p.: 108–110°; $[\alpha]_D$: +25°; IR: 3039, 1663 (Δ⁴), 1706 (C=O), 900, 890, 838 (OSi≡(CH_3)$_3$); NMR: 5.38 (4-H), 2.16 (21-CH_3), 0.90 (18-CH_3), 0.12 (OSi≡(CH_3)$_3$).

17β - Hydroxy - 19 - nor - 17β - H - pregnan - 20 - one (**3**). Compound **3** was prepared according to the same procedure from the corresponding 17-ethinyl compound as described for **1**; yield: 70%. Crystallisation from acetone gave the analytical sample; m.p. 156–158°; $[\alpha]_D$: +16°; IR (CH_2Cl_2): 1701 (C=O), 3610 (OH); NMR: 2.55 (21-CH_3), 0.93 (18-CH_3). (Found: C, 78.7; H, 10.8. Calc. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; O, 10.51%).

17β - Hydroxy - Δ⁴ - 19 - nor - 17β - H - pregnen - 20 - one 17β - acetate (**12**). Compound **1** (10.0 g) was suspended in EtOAc (300 ml), subsequently Ac_2O (13.0 ml) and dinitrobenzene sulfonic acid (0.10 g) were added. The steroid dissolved while stirring and the mixture was kept at room temp. for 1 hr, then neutralised with pyridine. Working up was done by extraction. The crude product (10.5 g) was crystallised from acetone, yield: 8.5 g of **12**; m.p.: 137–139°. Analytical sample: m.p.: 140–142°; $[\alpha]_D$: +35°; IR: 3038, 1662 (Δ⁴), 1738, 1256, 1246, 1041 (OAc), 1711 (CO) (Found: C, 76.7; H, 9.4. Calc. for $C_{23}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93%).

Acetylation of **1** with Ac_2O and pyridine at reflux temp. did not give the expected acetate **12** but a mixture of two other products, which could be separated by chromatography (100 parts silicagel "Woelm"):

(a) *17aα - Methyl - 17aβ - hydroxy - Δ⁴ - D - homo - estren - 17 - one* (**11b**). Crystallisation from acetone gave the pure product: m.p.: 137–139°; $[\alpha]_D$: +8°; IR: 3040, 1668 (Δ⁴), 1714 (C=O), 3487 (OH); NMR: 5.41 (4-H), 1.32 (17a-CH_3), 0.77 (18-CH_3); mass: 302 (parent; 100%), 259 (21%), 215 (89%).

(b) *The 17aβ-acetate of* **11b**. Crystallisation from acetone gave the pure product; m.p.: 203–207°; $[\alpha]_D$: +40°; IR: 3041, 1668 (Δ⁴) 1729 (C=O), 1758, 1246 (OAc); NMR: 5.42 (4-H), 2.07 (17aβ-OAc), 1.80 (17aα-CH_3), 0.87 (18-CH_3). (Found: C, 76.9; H, 9.4. Calc. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93%).

B. *Rearrangement of 17β - hydroxy - Δ⁴ - 19 - nor - 17β - H pregnen - 20 - one* (**1**) (*Fig. 1*)

Sodium hydride—55% dispersion in oil—(0.43 g) was suspended in dry DMSO (9 ml) in a N_2 atmosphere and the temp. was raised to 70°. Stirring was continued for 45 min at this temp. while H_2 evolved. The mixture was cooled to room temp. and a soln of methyl triphenylphosphoniumbromide (3.55 g) in DMSO (16 ml) was added. After 5 min a soln of **1** (1.0 g) in dry THF (10 ml) was added.

The temp. was raised to 70° and stirring continued for 3 hr. After cooling to room temp. the mixture was worked up by extraction. The crude product, a mixture of two compounds, was chromatographed on silicagel "Merck G" (160 g). Compound **4a** was obtained in a pure state (0.06 g). IR: 3038, 1660 (Δ⁴), 3083, 1640, 898 (=CH_2), 3609 (OH); NMR: 5.38 (4-H), 4.38 (17-CH_2), 4.79 (17-CH_2), 1.27 (17a-CH_3), 0.77 (18-CH_3). (Found: C, 83.9; H, 10.9. Calc. for $C_{21}H_{32}O$: C, 83.94; H, 10.73; O, 5.32%). The isomer **4b**, could not be obtained in a pure state; it was contaminated with **4a**.

C. *Reactions on 17β - hydroxy - 19 - nor - 17β - H - pregnan - 20 - one* (**3**)

(a) Compound **3** was treated as described in Section B; working up and subsequent chromatography yielded the epimers **7a,b**. One epimer, **7a**, was obtained pure in a yield of 40%; m.p. 136.5–137.5°; $[\alpha]_D$ −+49°; IR (CH_2Cl_2): 3090, 1643 (=CH_2), 3619 (OH); NMR (90 MHz): 1.29 (17aβ-CH_3), 0.75 (18-CH_3), 4.85 Hz (=CH_2). (Found: C, 83.5; H, 11.4. Calc. for $C_{21}H_{34}O$: C, 83.38; H, 11.33; O, 5.29%). The second epimer, **7b**, could be obtained pure by crystallisation from MeOH-EtOAc; yield: 2.5%. M.p.: 111–112°; $[\alpha]_D$ −+23°; IR (CH_2Cl_2): 3082, 1641 (-CH_2), 3617 (OH); NMR: (90 MHz): 1.31 (17aα-CH_3), 0.80 (18-CH_3), 4.72 and 4.92 (=CH_2).

(b) *Ozonisation of 17aβ - methyl - 17,17 - methylene - D - homo - 5α - estran - 17aα - ol* (**7a**). A soln of **7a** (1.0 g) in CH_2Cl_2 (60 ml) was treated with O_3 (5% in oxygen) at −70° during 20 min and subsequently at that same temp. during 10 min with O_2.

After warming up to room temp. the mixture was treated with AcOH (60 ml) and Zn powder (2 g). After stirring for 1.5 hr the mixture was poured into water (2000 ml) and extracted with CH_2Cl_2. Working up and subsequent crystallisation from n-hexane yielded an unidentified acid-yield: 44%-; chromatography of the mother liquor yielded, after crystallisation from n-hexane, compound **10a**. M.p. 187–188°; $[\alpha]_D$ −+19°; IR (CH_2Cl_2): 1719 (C=O), 3616 (OH); NMR: 1.18 (17aβ-CH_3), 0.70 (18-CH_3). (Found: C, 79.1; H, 10.7. Calc. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; O, 10.51%).

For further identification the acid obtained (0.113 g)—mass: M^+ = 320.3 (36%), M^+-$COCH_3$ = 277.2 (99%)—was treated with LAH (0.100 g in 10 ml of THF). After stirring for 20 hr at room temp. water was added (0.4 ml). The resulting soln was filtered and

the filtrate was poured out into water and extracted with CH_2Cl_2. After working up and subsequent crystallisation from acetone, **8** was obtained in a yield of 35%. NMR: 3.73 (one proton, quartet, J = 6 Hz, –CHOHCH$_3$), 3.54 (two protons, –CH$_2$OH), 1.02 (three protons, doublet, J = 6 Hz, –CHOHCH$_3$), 0.62 (singlet, 18-CH$_3$).

D. *Reactions on 17β - hydroxy - Δ⁴ - 19 - nor - 17β - H - pregnen - 20 - one 17β - trimethylsilyl ether* (**2**) (*Fig. 1*)

(a) *With methylene triphenylphosphorane in DMSO.* Sodium hydride—55% dispersion in oil—(1.80 g) was suspended in dry DMSO (60 ml) in a N_2 atmosphere and the temp. raised to 70°. Stirring was continued for 45 min at this temp. After cooling to 25° a soln of methyl triphenylphosphoniumbromide (19.2 g) in DMSO (90 ml) was added in 15 min and stirring was continued for another 15 min. A soln of **2** (5.61 g) in toluene (55 ml) was added and the temp. raised to 70°. After 2 hr no starting material was left according to TLC. Working up was done by extraction with n-hexane. The silyl ether was split off in MeOH with *p*-toluene sulfonic acid.

The crude product consisted of about 7 products of which **4a,b**, **5** and **11a,b** could be identified by TLC.

(b) *With methylene triphenylphosphorane in toluene.* A suspension of methyl triphenylphosphoniumbromide (14.4 g) in dry toluene (60 ml) was added to n-BuLi (26 ml; 1.15 mol in n-hexane) in a N_2 atmosphere. The mixture was refluxed for 2 hr. After cooling to 25° a soln of **2** (3.74 g) in dry toluene (30 ml) was added. The mixture was refluxed for 24 hr, after which still some starting material was present. After working up and splitting off the silyl ether the starting material was separated by filtration through silicagel. The product was crystallised from acetone–hexane giving pure **5** (0.12 g); m.p.: 103–105°; $[\alpha]_D$: +31°; IR: 3618, 997 (OH); 3039, 1664 (Δ⁴); 3081, 1634, 898 (=CH$_2$); NMR: 5.40 (4-H), 4.85 (CH$_2$), 1.83 (21-CH$_3$), 0.97 (18-CH$_3$). (Found: 83.9; H, 10.8. Calc. for $C_{21}H_{32}O$: C, 83.94; H, 10.73; O, 5.32%).

(c) *With methylene triphenylphosphorane in pyridine.* Methyl triphenylphosphoniumbromide (250 g) was suspended in dry pyridine while N_2 was passed over; n-BuLi (288 ml; 2.23 mol in n-hexane) was added in 20 min, while the temp. rose from 20° to 45°. The mixture was heated to reflux—85°—and stirred for an additional 15 min during which all material dissolved and n-butane evolved. Then **2** (43.5 g) in dry toluene (200 ml) was added, and reflux was continued for 2 hr. The reaction was worked up by extraction with n-hexane. The silyl ether was split off in acetone with 2N HCl.

Extraction with CH_2Cl_2 and evaporation of the solvent gave a residue of 65 g. Chromatography on silicagel "Woelm" with toluene/hexane 50:50 gave 20 g of triphenylphosphine; m.p.: 82–83°. Subsequent elution with toluene/EtOAc gave **5** (22 g) contaminated, however, with a by-product (**11b**) with the same R_f value.

Separation of the two compounds could be achieved by treating the mixture with $NaBH_4$ and subsequent column chromatography. The isopropenyl compound **5** was crystallised from MeOH; yield: 12 g; m.p.: 100–102°.

E. *Rearrangements of 17β - hydroxy - Δ⁴ - 19 - nor - 17β - H - pregnen - 20 - one 17β - acetate* (**12**) (*Figs. 3 and 5*)

(a) *With methylene triphenylphosphorane in DMSO.* Sodium hydride - 55% dispersion in oil—(0.16 g) was suspended in dry DMSO (4.3 ml) in a N_2 atmosphere and the temp. was raised to 70°. After 45 min the mixture was cooled to 25° and methyl triphenylphosphoniumbromide (1.47 g) dissolved in dry DMSO (6 ml) was added. After 10 min a soln of **12** (0.516 g) in dry THF (10 ml) was added, and stirring was continued at 70° for 2.5 hr. Working up was done by extraction and gave a residue of 1.3 g; subsequent chromatography gave two pure products. The first was crystallised from acetone, yielding **15** (0.22 g); m.p.: 231–235°; $[\alpha]_D$: +119°; ϵ_{220}: 11.100; IR (CH_2Cl_2): 1661, 808 (Δ⁴), 1742 (C=O), 1635 (C=C in 5-ring); NMR: 5.69 (HC=C, J = 1.5 Hz), 5.45 (4-H), 2.13 (d, J = 1.5 Hz, CH$_3$–C=C), 1.09 (18-CH$_3$). (Found: C, 80.7; H, 9.3. Calc. for $C_{23}H_{30}O_3$: C, 80.93; H, 9.26; O, 9.80%).

The second product could not be crystallised (**14**); IR: 3036, 1661 (Δ⁴), 1752 (C=O), 3600 (OH); NMR: 5.41 (4-H), 2.53 (J_{AB} = 13 Hz, H_2C–C=), 1.63 (CH$_3$ next to ether), 0.93 (18-CH$_3$).

(b) *With methylene triphenylphosphorane in toluene.* Methyl triphenylphosphoniumbromide (7.43 g) was added to a soln of n-BuLi (16 ml; 1.15 mol in n-hexane) in dry toluene (75 ml) in a N_2 atmosphere. The mixture was heated under reflux for 1.5 hr and a soln of **12** (4.22 g) in dry toluene (25 ml) was added in 5 min. Stirring was continued for 3.5 hr, then the mixture was cooled to room temp. and worked up by extraction. The crude product (6.1 g) was purified by chromatography over silicagel (300 g). After crystallisation from methyl cyanide pure **13** was obtained: m.p.: 136–137°; $[\alpha]_D$: +32°; ϵ_{236}: 6.150; IR: 3039, 1663 (Δ⁴), 1659 (Δ¹⁶), 1677 (C=O), 3453 (OH); NMR: 6.04 (dd, 16-H), 5.45 (4-H), 1.07 (18-CH$_3$); mass: 286 (parent). Compound **13** was further characterised through its acetate: 17 - hydroxy - Δ⁴'¹⁶ - D - homo-estradien - 17a - one 17-acetate; m.p.: 142–143°; NMR: 6.47 (dd, 16-H), 5.45 (4-H), 2.20 (OAc), 1.13 (18-CH$_3$).

(c) *With sodium hydroxide in DMSO.* Compound **12** (2.5 g) was dissolved in dry DMSO (60 ml) and a catalytic amount of NaOH powder was added. After 2.5 hr standing at room temp. the mixture was neutralised with AcOH and diluted with ice-water. The ppt was sucked off, dried and purified by chromatography over silicagel. Subsequently were isolated: **12**, **14** (in minor quantities) and **16**; compound **16**: m.p.: 209–212°; $[\alpha]_D$: +24°; IR (CH_2Cl_2): 1665, 811 (Δ⁴), 1774 (5-membered lactone), 3600 (OH); NMR: 5.44 (4-H), 2.63 (–AB–J_{AB} = 17 Hz, CH$_2$ in lactone ring), 1.51 (CH$_3$ in lactone ring), 1.00 (18-CH$_3$). (Found: C, 76.6; H, 9.5. Calc. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93%).

(d) *With sodium hydride in DMSO.* Sodium hydride (0.12 g)—55% dispersion in oil—was suspended in dry DMSO (5 ml) in a N_2 atmosphere and the temp. was raised to 70°. After 40 min the mixture was cooled to room temp. and a soln of **12** (1.0 g) in dry DMSO (15 ml) was added. Stirring was continued for 1 hr, then the mixture was poured out into ice-water and the ppt was sucked off. Chromatography of the crude product over silicagel yielded the spiro-compounds **14** and **15**.

F. *Rearrangements of 3β,17α - dihydroxy - Δ⁵ - pregnen - 20 - one 17α-acetate* (**17**) (*Fig. 5*)

(a) *With sodium hydride in DMSO.* Compound **17** (3.74 g) was treated in the same way as described under section E,d. The main product was crystallised from MeOH giving **20** (m.p.: 262–264°), which was characterised through its 3β-acetate: m.p.: 236–238°; $[\alpha]_D$: –147°; ϵ 11.100; IR (CH_2Cl_2): 1670 (Δ⁵), 1730, 1246, 1032 (3-OAc), 1743, 964 (5-membered lactone), 1632 (conj. C=C); NMR: 5.42 (6-H), 5.83 (quartet, J = 1.5 Hz, CH$_2$ in lactone), 4.61 (3-H), 2.13 (d, J = 1.5 Hz, CH$_3$ in lactone), 2.02 (OAc), 1.03 (19-CH$_3$), 0.93 (18-CH$_3$); mass (compound **20**): 356 (parent, 28%), 338 (57%), 323 (61%).

(b) *With sodium hydroxide in DMSO.* Compound **17** (3.71 g) was treated as described under E,c and the product was acetylated for structure elucidation giving **19**; m.p. 256–259°; $[\alpha]_D$: –70°; IR (CH_2Cl_2): 1670 (Δ⁵), 1728, 1249, 1030 (3-OAc), 1775, 963 (5-membered lactone), 3607 (OH); NMR: 5.41 (6-H), 4.60 (3-H), 2.48 (J_{AB} = 9 Hz, CH$_2$ in lactone), 2.03 (3-OAc), 1.53 (CH$_3$ in lactone), 1.02 (19-CH$_3$), 0.97 (18-CH$_3$). Treatment of **19** (0.050 g) with NaOH (0.05 g) in MeOH (0.5 ml) for 3 hr at 40° gave after working up **20**.

(c) *With methylene triphenylphosphorane in DMSO.* Sodium hydride—55% dispersion in oil—(1.2 g) was suspended in dry DMSO (40 ml) in a N_2 atmosphere and the temp. was raised to 70°. After 45 min the mixture was cooled to 25° and methyl triphenylphosphoniumbromide (14.4 g) dissolved in dry DMSO (60 ml) was added. After 20 min a soln of **17** (8.32 g) in dry THF (60 ml) was added, and stirring was continued at 70° for 10 min. Working up was done by extraction. Column chromatography of the residue yielded compound **19**.

(d) *With methylene triphenylphosphorane in toluene.* Methyl triphenylphosphoniumbromide (6.1 g) was added to a soln of n-BuLi (7.5 ml; 2.25 mol in n-hexane) in dry toluene (75 ml) in a N_2 atmosphere and the mixture was refluxed for 1.5 hr, then cooled to 50°. Compound **17** (3.74 g; 3β-acetate) was added and the temp. was raised to reflux. Stirring was continued for 1 hr, then the

reaction was worked up by extraction. Subsequent chromatography gave two products: the spiro-ether **18** m.p.: 203-205°; $[\alpha]_D$: -54°; IR (CH_2Cl_2): 1670 (Δ^5), 1727, 1240, 1034 (3-OAc), 1749, 1405 (C=O), 3582 (OH); NMR: 5.41 (6-H), 4.61 (3-H), 2.03 (OAc), 1.67 (CH_3 next to the ether), 1.03 (19-CH_3), 0.78 (18-CH_3); mass: 416 (parent, 44%), 356 (100%), 338 (73%); and the 3β-alcohol **17**.

Treatment of **18** (0.05 g) with NaOH (0.05 g) in MeOH (0.5 ml) for 3 hr at 40° gave after working up **21** (0.038 g); IR (CH_2Cl_2): 1606, 963, 955 (C=C), 1688 (C=O, 2x), 3608 (OH); NMR: 5.41 (H-C=C), 5.38 (6-H), 2.21 (CH_3 in side-chain), 1.03 (19-CH_3), 0.93 (18-CH_3); mass: 356 (parent).

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