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STEROIDAL ANALOGUES OF UNNATURAL CONFIGURATION—X[1]

SYNTHESIS OF 9-METHYL-19-NOR-9β,10α-PROGESTERONE

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Abstract—The reaction of 3,3-ethylenedioxy-9-methyl-9β-oestr-5(10)-en-17-one (**4**) with tosylmethyl isocyanide and base afforded the 17β- and 17α-carbonitriles (**5** and **6**). Treatment of the 17β-epimer (**5**) with methyl lithium gave, after hydrolysis, 9-methyl-19-nor-9β-pregn-5(10)-ene-3,20-dione (**8**). The same reaction sequence employed on 3,3; 5,5-bisethylenedioxy-9-methyl-4,5-seco-9β,10α-oestr-17-one (**12**), with subsequent cyclization, yielded the 5β-hydroxy-3,20-diketones (**17** and **18**) as well as 9-methyl-19-nor-9β,10α-progesterone (**19**) and its 17α-epimer (**20**).

The synthesis of steroids possessing the 9 - methyl - 19 - nor - 9β,10α - skeleton [19(10→9β)*abeo* - 10α - steroids] has hitherto been confined to the testosterone analogue (**1**) and some of its derivatives.[2,3] Following a report[2] from this laboratory on the total synthesis of **1**, the compound has also been prepared by Coombs *et al.*,[3] using the same method of stereoselective introduction of the 9β-methyl group. The structure of **1** has since been confirmed by X-ray crystallography.[4]

In view of our continuing interest in the properties of skeletally modified steroids, the synthesis of further analogues of the natural steroidal hormones was undertaken. We now report the synthesis of 9 - methyl - 19 - nor - 9β,10α - progesterone (**19**), through the application of a novel method[5] for converting 17-oxo- to 17-acetyl steroids.

Treatment of 17β - hydroxy - 9 - methyl - 9β,10α - oestr-4 - en - 3 - one (**1**) with ethylene glycol–*p*-TsOH under standard conditions afforded a mixture of acetals, which was readily separated by chromatography and shown to comprise the Δ^5-isomer (**2**; 44·5%) (olefinic H at δ 5·28 in NMR) and the $\Delta^{5(10)}$-isomer (**3**; 52%) (no olefinic H in NMR). Acetalization of 19-nortestosterone under similar conditions has also been shown[6] to give a mixture of double bond isomers.

Treatment of the mixture of **2** and **3** under more vigorous acetalization conditions (longer reaction periods at higher temperature and catalyst concentration) resulted in the exclusive formation of the $\Delta^{5(10)}$-isomer (**3**). In view of ensuing difficulties in regenerating the Δ^4-3-one system by conventional hydrolysis of a $\Delta^{5(10)}$-3-acetal in this series, reaction conditions were sought for the selective formation of the Δ^5-isomer (**2**) from **1**. Despite extensive experimentation this was unsuccessful since the most favourable result, obtained by treatment of **1** with 0·01% *p*-TsOH in benzene under gentle reflux for 30 minutes, afforded a mixture, shown by GLC (OV-210, 210→240°), to contain **2** and **3** in the ratio 5:3. More prolonged reaction resulted in a slow increase of **3** at the expense of **2**.

Exchange acetalization of **1** using 2-ethyl-2-methyl dioxolane,[7] also resulted in preferential formation of **3**, while acetalization in the presence of fumaric acid as catalyst[8] afforded a mixture of products, which was shown by GLC to contain the presumed Δ^4-3-acetal (**9**; *ca.* 42%) together with **2** (*ca.* 15%), **3** (*ca.* 6%) and starting material (**1**; *ca.* 30%).

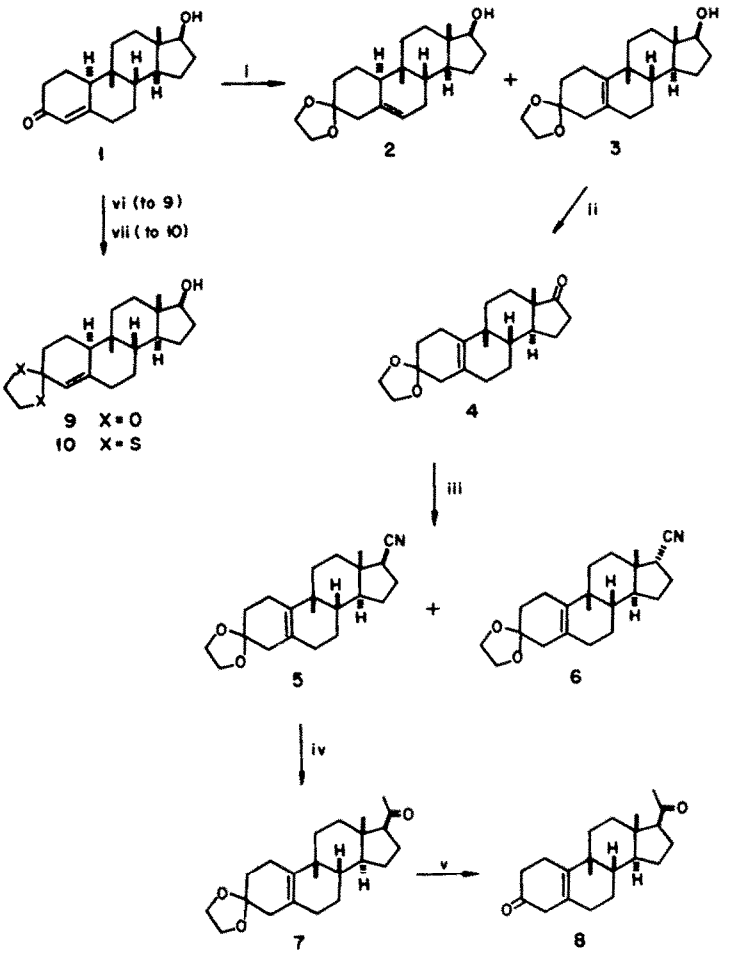
With the exception of the method leading to exclusive formation of **3**, the quantitative results of the acetalization experiments were difficult to reproduce.

Oxidation of the crude 17β - hydroxy - $\Delta^{5(10)}$ - compound **3** with CrO_3-pyridine afforded the 17-ketone (**4**; 88% from **1**). Treatment of **4** with tosylmethyl isocyanide (TosMIC), as described in the preceding paper,[5] afforded a mixture (89%) of the 17β- and 17α-carbonitriles (**5** and **6** resp). The epimer ratio was estimated by GLC (OV-17, 230→280°), and by intensity measurements of the 13β-Me signals (at δ0·97 and 0·86 for **5** and **6** resp) in an NMR spectrum of the mixture,[5,9] to be *ca.* 86:14. This significant deviation from the isomer distribution obtained by TosMIC treatment of androstan-17-ones (*ca.* 70:30),[5] could be the result of a long-range effect of the *B,C-cis* ring junction upon 17-protonation. Mild alkaline treatment (methanolic 0·1*N* KOH at 25° for 16 hr) of a small portion of this mixture resulted in a change of the epimer ratio 5:6 to 72:28. The failure of more prolonged alkaline treatment to affect this ratio suggested that it is the equilibrium position for the 17-epimers.

Recrystallization of the mixture of **5** and **6** from methanol afforded the pure 17β-isomer (**5**; 59% based on **4**). A further 8% of **5** was recovered by recrystallization of the product obtained by equilibration of the mother-liquor residues. This procedure was less productive than crystallization of the initial reaction product, owing to the change in epimer ratio. Chromatography of the final mother liquor residues, now enriched to the extent of 42% in the minor isomer, afforded that product (**6**; 8%) and further **5** (12%).

Treatment of the 17β-carbonitrile (**5**) with methyl lithium, followed by hydrolytic work-up, afforded the 20-ketone (**7**) in excellent yield. As expected,[5] these conditions did not result in any epimerization of the 17-position. The acetal function of **7** was hydrolysed under mild conditions with aqueous acetic acid to give the $\Delta^{5(10)}$-3,20-dione (**8**) as an unstable oil.

It was expected that isomerization of the $\Delta^{5(10)}$-bond of **8** into conjugation would proceed smoothly to give the target molecule (**19**). However, treatment with methanolic potassium hydroxide under nitrogen and at various temperatures resulted only in extensive decomposition of **8**. Attempted isomerization under acidic conditions was also unsatisfactory. For example, the compound **8** remained unchanged after exposure to *M*-perchloric acid in THF at 25° for 90 min, while more prolonged exposure



i $(CH_2OH)_2$–*p*·TsOH ii CrO_3–C_5H_5N iii TosMIC-t-BuOK
iv MeLi v AcOH–MeOH–H_2O vi $(CH_2OH)_2$-Fumaric acid
vii $(CH_2SH)_2$–BF_3·OEt_2

(overnight) afforded no more than *ca.* 20% of **19** (estimated from TLC), together with starting material and intractable degradation products. The compound **7** was completely destroyed after 24 hr in 90% acetic acid at 100°.

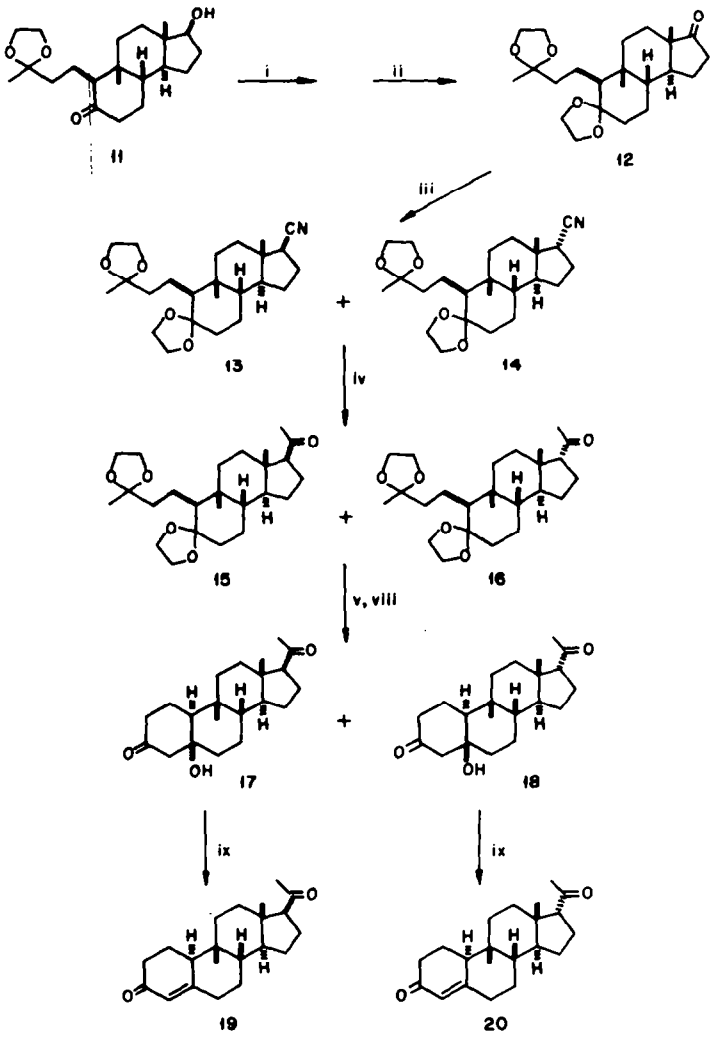
This unexpected difficulty suggests either that the equilibrium **8** ⇄ **19** favours the deconjugated compound, or that conjugation is strongly inhibited in this skeleton by steric hindrance to protonation at the 10-position. There is some analogy for the former proposal in the work of Bucourt.[10] It has been shown that the energetically favoured displacement of an olefinic bond from the 5(10)- to the 4-position in the natural (all *trans*-) steroids is partly governed by conformational transmission effects acting in concert from both extremities of the molecule. By contrast the effect of the *C,D-trans* ring junction in a 19-nor-8α-steroid, where the *B*- and *C*-rings are *cis*-fused, opposes the stabilization of a Δ^4-bond, and a relatively greater proportion of the $\Delta^{5(10)}$-isomer is formed under equilibration conditions. The same argument should apply qualitatively to the 19-nor-9β-methyl-series, where the *B*- and *C*-rings are also *cis*-fused. However, it is unlikely that a completely unfavourable equilibrium prevails in the case of **8**, since a sample of the neat oil, stored for several months at room temperature, underwent appreciable conversion to the Δ^4-isomer **19**. The time factor and concomitant decomposition of a large part of the sample rendered this method impractical as a route to **19**. The lability of **8** is clearly due to the high reactivity of the 4-position, which is susceptible to autoxidation.[11]

The role of steric hindrance to protonation at C(10) in the dienolate derived from **8** is uncertain, but it has been shown[2] that α-alkylation of a des-*A*-9β-methyl-5-one occurs exclusively at C(6) rather than at C(10) although the 5(10)-enolate is predictively favoured. It is therefore probable that both steric and thermodynamic factors are responsible for the difficulty in converting **8** to **19**.

In view of this obstacle, alternative routes to **19** were sought. Initially, some attention was given to different methods of protecting the *A*-ring of **1**. The Δ^4- and Δ^5-3-acetals (**9** and **2** resp) were regarded as unsatisfactory in view of the lack of selectivity in their preparation and it was considered that protected dienyl derivatives (e.g. the dienyl ether of **1**) might be too labile to survive successive oxidation, TosMIC treatment, and alkylation.

Although BF_3-catalysed treatment of **1** with ethanedithiol afforded the Δ^4-3-dithioacetal (**10**) in excellent yield, the attempted regeneration of the Δ^4-3-one was less successful. Several recently described methods[12] were examined, but the yields were not good enough to justify the use of **10** as an intermediate.

The problem of protecting the *A*-ring with suitable



viii KOH–MeOH
ix *p*·TsOH–C_6H_6

functionality for regenerating the Δ^4-3-one was circumvented by carrying out the desired *D*-ring transformations on a tricyclic precursor of **1**, from which the *A*-ring was formed subsequently.

The seco-steroid[3] (**11**) was converted to the corresponding bis-acetal, which was not characterized, but directly oxidized with CrO_3-pyridine to the 17-ketone (**12**; 60% from the Δ^9-5-oxo-precursor of **11**). This product (**12**) was treated with TosMIC[5] to give a mixture of the 17-carbonitriles (**13** and **14**) containing 84% of the major isomer (**13**), as shown by GLC (OV-101, 225°) and NMR.[5] Although the pure 17β-isomer (**13**) could be isolated by crystallization, the mixture of **13** and **14** was treated with methyl lithium in THF to give the corresponding mixture of 20-ketones (**15** and **16** resp). Chromatography of a portion of this material revealed that separation of the isomers was possible at this stage, although the 17α-acetyl compound (**16**) was slightly contaminated with an unidentified impurity.

Our initial approach to carrying out the remaining steps of the sequence was based upon using the above mixture of 20-ketones (**15** and **16**), since it was expected that partial equilibration would occur at the 17-position under the conditions to be used for closure of the *A*-ring. Acid hydrolysis of the mixture, followed by alkaline treatment of the resultant trione afforded a chromatographically inseparable 4:1 mixture of **19** and **20** (28%) together with the 5β-hydroxy-3,20-diketones (**17** and **18**) (14 and 3·5% resp; all yields from **12**) which were readily separated.

Crystallization of the mixture of **19** and **20** afforded pure 9-methyl-19-nor-9β,10α-progesterone (**19**) (50% recovery). Attempts to recover further material through equilibration of the mother-liquor residues (**19**:**20** ratio of *ca.* 60:40) were unsuccessful, owing to decomposition arising from concomitant enolization of the Δ^4-3-one moiety (cf. lability of **8**).

The CD spectrum of **19** (Fig. 1) showed that, although the Cotton effect of the 3-CO group is partly obscured, the characteristic transitions of the Δ^4-3-one chromophore in the 9β,10α-skeleton[13] are present, together with that for a 17β-acetyl group.[14]

In view of the discrepancy between the $\Delta\epsilon$ value for the $\pi \rightarrow \pi^*$ transition of **19** and that published[2] for **1**, the latter compound was re-examined. The previously recorded value was determined on an instrument which gave inferior spectra at low wavelength, and the data recorded here [$\Delta\epsilon$ −15·8 and +2·2 (at 243 and 315 nm resp)] (Fig. 1) are considered to be more accurate.

The assignment of 5β-stereochemistry to the two hydroxy-diketones (**17** and **18**) was made upon the basis of

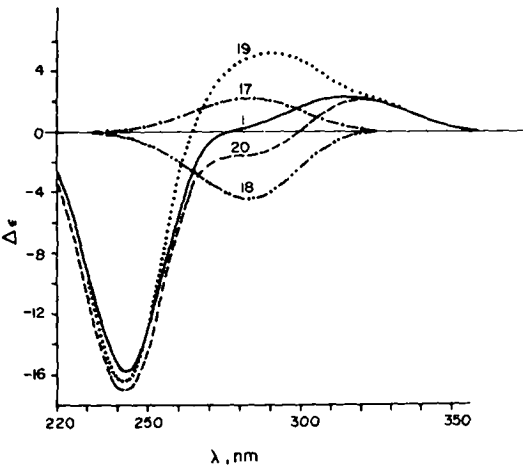


Fig. 1. CD spectra of the compounds **1**, **17**, **18**, **19** and **20**.

the excessive steric demand for bond-forming β-face approach of the Δ^3-enolate to the 5-position in the intermediate triketone. This would necessitate closure 1,3-diaxially to the 9β-methyl group. By contrast, α-face approach to generate a 5β-hydroxy-group is relatively unhindered.

The more abundant hydroxy-diketone (**17**) was logically assigned 17β-stereochemistry and, in accordance with the findings of Rubin and Blossey,[15] the NMR signal for the 13β-Me group of this isomer appeared at higher field (δ 0·68) than that (δ 0·90) of the minor 17α-isomer (**18**). Furthermore, the CD spectra of **17** [Δε + 2·2 (283 nm)] and **18** [Δε − 4·4 (283 nm)] indicated that, notwithstanding the contribution of the 3-CO group,[16] the relative signs of the Cotton effects of the respective 20-CO groups were compatible with the assignments.[14]

Careful treatment of **17** with *p*-TsOH in benzene-methanol at 20° afforded the Δ^4-3,20-diketone (**19**) in good yield, without any epimerization at the 17-position. A trace impurity was shown by GLC (OV-101, 225°) to be the $\Delta^{5(10)}$-isomer **8**.

The minor isomer (**18**) underwent similar β-elimination to give the 17α-acetyl compound **20**. This product displayed the expected[14] negative Cotton effect [Δε − 1·7 (281 nm; infl.)] for the 20-CO group (Fig. 1) and the NMR spectrum exhibited characteristic[16] deshielding of the 13β-Me group (δ 1·00) relative to the same signal (δ 0·71) in the 17β-acetyl compound (**19**).

In view of the modest recovery of the target molecule (**19**) by recrystallization of the mixture of **19** and **20** obtained in the sequence in which intermediate isomers were not separated, an alternative and more efficient route was developed. Thus, the 17β-acetyl bis-acetal (**15**) was separated from the aforementioned mixture of **15** and **16**, and carefully hydrolysed with aqueous acetic acid in methanol. Subsequent mild alkaline treatment (methanolic 0·1*N* KOH at r.t.) resulted in only *ca.* 5% epimerization at the 17-position. Chromatography of the product afforded the uncyclized 3,5,20-triketone (13%), **17** (38%), **18** (*ca.* 2%) and a mixture of **19** and **20** (27%). The more favourable epimer distribution of this mixture resulted in the recovery of 85% of **19** by crystallization. By combining this with the material obtained through the efficient dehydration of **17**, a total yield of 37% of **19** (from **12**) was obtained. Recycling the recovered 3,5,20-triketone would improve this yield by a further 7–8%. By contrast, the sequence in which separation of the epimers was postponed until the last step resulted in a 27% yield of the product **19** (based on **12**).

EXPERIMENTAL

For general directions see Ref. 5.

Acetalization of 9 - *methyl* - 19 - *nor* - 9β,10α - *testosterone* (**1**). The enone **1** (947 mg), *p*-TsOH (20 mg) and ethylene glycol (6 ml) in benzene (100 ml) were refluxed gently for 16 hr in a Dean and Stark apparatus. After the addition of sat $NaHCO_3$aq (2 ml), work-up (benzene extraction and NaClaq) afforded an oil (1·3 g). Adsorption of part (90 mg) of the oil on silica gel (14 g) and elution with benzene–EtOAc(2:3) gave 3,3 - ethylenedioxy - 9 - methyl - 9β,10α - *oestr* - 5 - *en* - 17β - *ol* (**2**; 34 mg), which crystallized from benzene incorporating 0·5 mol equiv solvent of crystallization, m.p. 75–80°, $[\alpha]_D$–12° (*c* 1·2), ν_{max} 3600 cm^{-1}, δ 0·79 (3H, s, 13β-Me), 0·88 (3H, s, 9β-Me), 3·65 (1H, t, J 8 Hz, 17α-H), 3·92 (4H, s, 3-acetal), 5·28 (1H, br.d, J 5 Hz, 6-H) and 7·34 (3H, s, 0·5 C_6H_6) (Found: C, 77·3; H, 9·4; M^+, 332 and 78. $C_{21}H_{32}O_3 \cdot 0{\cdot}5C_6H_6$ requires: C, 77·6; H, 9·5%; M, 332 and 78). Further elution with the same solvent gave 3,3 - *ethylenedioxy* - 9 - *methyl* - 9β - *oestr* - 5(10) - *en* - 17β - *ol* (**3**; 40 mg), m.p. 154–157° (from Et_2O), $[\alpha]_D$–95° (*c* 1·0), ν_{max} 3600 cm^{-1}, δ 0·80 (3H, s, 13β-Me), 1·06 (3H, s, 9β-Me), 3·67 (1H, t, J 8 Hz, 17α-H) and 3·97 (4H, s, 3-acetal) (Found: C, 76·15; H, 9·7; M^+, 332. $C_{21}H_{32}O_3$ requires: C, 75·9; H, 9·7%; M, 332).

Treatment of the remaining oily mixture (2 + 3; 1·21 g) as before, but using 60 mg *p*-TsOH, under vigorous reflux for 16 hr afforded an oil (1·3 g) containing only the $\Delta^{5(10)}$-isomer **3** (by TLC).

3,3-*Ethylenedioxy*-9-*methyl*-9β-*oestr*-5(10)-*en*-17-*one* (**4**). The crude $\Delta^{5(10)}$-compound **3** (1·3 g) was added during 0·5 hr to a CrO_3-pyridine suspension [prepared by adding CrO_3 (3 gr) in portions to well stirred pyridine (30 ml) at 15–20°] at 10°. After stirring the mixture for 2 hr at 10° and 16 hr at 25°, ice and sat $NaHCO_3$aq were added. Work-up [extraction with benzene-Et_2O (1:1) and NaClaq] afforded a yellow-brown oil (1·1 g) which was adsorbed on alumina (Act III, neutral: 50 g) and eluted with benzene-EtOAc (9:1) to give **4** (840 mg), m.p. 132–133·5° (from Et_2O), $[\alpha]_D$-44° (*c* 1·0), ν_{max} 1735 cm^{-1}, δ 0·92 (3H, s, 13β-Me), 1·09 (3H, s, 9β-Me) and 3·93 (4H, s, 3-acetal) (Found: C, 76·1; H, 9·0; M^+, 330. $C_{21}H_{30}O_2$ requires: C, 76·3; H, 9·15%; M, 330).

3,3 - *Ethylenedioxy* - 9 - *methyl* - 9β - *oestr* - 5(10) - *en* - 17β - *carbonitrile* (**5**). To a soln of **4** (600 mg) in DME (36 ml) under N_2, *M* t-BuOK–t-BuOH (18 ml) was added. A soln of TosMIC (710 mg) in DME (10 ml) was then added very slowly (during 2 hr) to the vigorously stirred mixture. After stirring for a further 1 hr the reaction was worked up (benzene extraction and NaClaq) to give a brown oil (1·15 g) which was adsorbed on alumina (Act I, neutral: 80 g). Elution with benzene-EtOAc (8:1) gave slightly yellow crystals (550 mg) of **5** and **6**, and 4-tosyloxazole[5] (62 mg). Crystallization of the mixture of **5** and **6** from MeOH afforded **5** (366 mg), m.p. 154–155°, $[\alpha]_D$–66° (*c* 0·3), ν_{max} 2240 cm^{-1}, δ 0·97 (3H, s, 13β-Me), 1·07 (3H, s, 9β-Me) and 3·95 (4H, s, 3-acetal) (Found: C, 77·3; H, 8·9; N, 4·2; M^+, 341. $C_{22}H_{31}NO_2$ requires: C, 77·4; H, 9·15; N, 4·1%; M, 341).

3,3 - *Ethylenedioxy* - 9 - *methyl* - 9β - *oestr* - 5(10) - *ene* - 17α - *carbonitrile* (**6**). The mother-liquor residue (184 mg) from the previous experiment was dissolved in 0·1 *M* KOH–MeOH. After 16 hr, work-up (benzene extraction and NaClaq) yielded a mixture from which **5** (51 mg) was isolated by crystallization (MeOH). The resultant mother-liquor residue (131 mg) was chromatographed on silica gel (33 g) with benzene-EtOAc (5:1) to give **6** (51 mg), m.p. 108–111° (cold MeOH), $[\alpha]_D$–122° (*c* 0·2), ν_{max} 2238 cm^{-1}, δ 0·86 (3H, s, 13β-Me), 1·08 (3H, s, 9β-Me) and 3·94 (4H, s, 3-acetal) (Found: C, 77·5; H, 9·3; N, 4·0%; M^+, 341) and **5** (68 mg).

3,3 - *Ethylenedioxy* - 9 - *methyl* - 19 - *nor* - 9β - *pregn* - 5(10) - *en* - 20 - *one* (**7**). MeLi (1·5 ml) was added to **5** (200 mg) in THF (20 ml) under N_2 at 25°. After 0·5 hr, sat NH_4Claq (2 ml) was added. Work-up (benzene extraction and NaClaq) gave an oil (247 mg) which was chromatographed on silica gel (25 g) with benzene-EtOAc (4:1) to give **7** (118 mg), m.p. 85–90° (from EtOH), $[\alpha]_D$–21° (*c* 1·1), ν_{max} 1698 cm^{-1}, Δε + 4·0 (286 nm), δ 0·66 (3H, s, 13β-Me), 1·05 (3H, s, 9β-Me), 2·08 (3H, s, 21-H_3) and 3·95 (4H, s, 3-acetal) (Found: C, 76·95; H, 9·5; M^+, 358. $C_{23}H_{34}O_3$ requires: C, 77·05; H, 9·6%; M, 358).

9-Methyl-19-nor-9β-pregn-5(10)-ene-3,20-dione (**8**). The acetal **7** (88 mg) in MeOH (6 ml) under N_2 was treated with aqueous 80% AcOH (10 ml) for 72 hr at 25°. Repeated azeotropic distillation *in vacuo* with benzene removed all traces of acid. Rapid chromatography of the residue (85 mg) on silica gel (16 g) with benzene-EtOAc (4:1) gave unstable **8** (48 mg) as a colourless oil, $[\alpha]_D$ −8° (*c* 1·0), ν_{max} 1701, shoulder at 1715 cm^{-1}, $\Delta\epsilon$ +2·7 (286 nm), δ 0·70 (3H, s, 13β-Me), 1·12 (3H, s, 9β-Me) and 2·10 (3H, s, 21-H_3) (Found: M^+, 314·2234. $C_{21}H_{30}O_2$ requires: M, 314·2246).

3,3-Ethylenedithio-9-methyl-9β,10α-oestr-4-en-17β-ol (**10**). The enone **1** (295 mg) in 1,2-ethanedithiol (0·75 ml) was treated with BF_3·Et_2O (0·02 ml). After stirring the mixture for 0·5 hr, work-up (benzene extraction, $NaHCO_3$aq and NaClaq) afforded a residue (290 mg) which was chromatographed on silica gel (45 g) with benzene-EtOAc (4:1) to give **10** (220 mg), m.p. 174–177°, $[\alpha]_D$−101° (*c* 1·1), ν_{max} 3610 cm^{-1}, δ 0·79 (3H, s, 13β-Me), 0·87 (3H, s, 9β-Me), 2·49 (1H, br.t, J 8 Hz, 10α-H), 3·32 (4H, m, 3-dithioacetal), 3·71 (1H, t, J 8 Hz, 17α-H) and 5·68 (1H, br.s, $w_{1/2}$5Hz, 4-H) (Found: C, 69·3; H, 9·0; S, 17·3; M^+, 364. $C_{21}H_{32}OS_2$ requires: C, 69·2; H, 8·85; S, 17·6%; M, 364).

3,3; 5,5 - Bisethylenedioxy - 9 - methyl - 4,5 - seco - 9β,10α - oestr - 17 - one (**12**). The crude ketone[3] **11** (4·7 g) in benzene (300 ml) containing *p*-TsOH (250 mg) and ethylene glycol (10 ml) was refluxed in a Dean and Stark apparatus for 4 hr. Addition of sat $NaHCO_3$aq and work-up (benzene extraction and NaClaq) gave an oily residue (5·0 g) which was oxidized with CrO_3-pyridine as described for the conversion of **3** to **4**. Chromatography of the product (4·8 g) on alumina (Act II–III, neutral: 350 g) using gradient elution [benzene → benzene-EtOAc (9:1)] gave **12** (3·3 g) as an oil. An analytical sample was obtained by distillation (130°; $4\cdot10^{-5}$ Torr), $[\alpha]_D$ +54° (*c* 1·2), ν_{max} 1734 cm^{-1}, δ 0·87 (3H, s, 13β-Me), 1·00 (3H, s, 9β-Me), 1·27 (3H, s, 4-H_3) and 3·70–4·10 (8H, m, 3- and 5-acetals) (Found: C, 70·2; H, 9·25; M^+, 392. $C_{23}H_{36}O_5$ requires: C, 70·4; H, 9·2%; M, 392).

3,3; 5,5-Bisethylenedioxy-9-methyl-4,5-seco-9β,10α-oestrane-17β-carbonitrile (**13**). To ketone **12** (3·0 g) and *M* t-BuOK-t-BuOH (80 ml) in DME (150 ml) under N_2 at 25°, TosMIC (3·0 g) in DME (10 ml) was added over 2 hr. After stirring the mixture for a further 1 hr, work-up (benzene extraction and NaClaq) afforded an oil (3·8 g). A portion (200 mg) of the oil was chromatographed on silica gel (65 g) with benzene-EtOAc (4:1) to give a mixture of **13** and **14** (115 mg) which was distilled (130°; $8\cdot10^{-5}$ Torr) to give an analytical sample, ν_{max} 2239 cm^{-1}, δ 0·86 ('0·45H', s, 13β-Me of **14**), 0·96 ('2·55H', s, 13β-Me of **13**) 1·01 (3H, s, 9β-Me), 1·30 (3H, s, 4-H_3) and 3·75–4·12 (8H, m, 3- and 5-acetals) (Found: C, 71·4; H, 9·0; N, 3·4; M^+, 403. $C_{24}H_{37}NO_4$ requires: C, 71·4; H, 9·2; N, 3·5%; M, 403). Crystallization from EtOH gave **13**, m.p. 157–160°, $[\alpha]_D$ +41° (*c* 0·8), ν_{max} 2239 cm^{-1}, δ 0·97 (3H, s, 13β-Me), 1·02 (3H, s, 9β-Me), 1·31 (3H, s, 4-H_3), 3·74–4·12 (8H, m, 3- and 5-acetals) (Found: C, 71·5; H, 9·45; N, 3·5%; M^+, 403).

3,3; 5,5-Bisethylenedioxy-9-methyl-19-nor-4,5-seco-9β,10α-pregnan-20-one (**15**). The crude mixture of **13** and **14** (3·6 g) in anhyd THF (100 ml) under N_2, was treated with MeLi (15 ml) for 0·5 hr. Addition of sat NH_4Claq (20 ml) and work-up (benzene extraction and NaClaq) gave an oil (3·6 g), of which a portion (300 mg) was chromatographed on silica gel (32 g) with benzene-EtOAc (4:1) to give **15** (198 mg), m.p. 114–117° (from MeOH), $[\alpha]_D$ +64° (*c* 0·8), ν_{max} 1698 cm^{-1}, δ 0·63 (3H, s, 13β-Me), 0·97 (3H, s, 9β-Me), 1·30 (3H, s, 4-H_3), 2·09 (3H, s, 21-H_3) and 3·74–4·12 (8H, m, 3- and 5-acetals) (Found: C, 71·3; H, 9·8; M^+, 420. $C_{25}H_{40}O_5$ requires: C, 71·4; H, 9·6%; M, 420). Further elution with the same solvent gave a product (probably **16**; 47 mg) (M^+, 420) contaminated with unidentified material (same R_f on TLC).

Hydrolysis and cyclization of the mixture of 17-acetyl compounds (15 and 16). The crude mixture of **15** and **16** (3·3 g) in MeOH (75 ml) under N_2 was treated with aqueous 80% AcOH (125 ml) for 50 hr at 25°. The mixture was diluted with H_2O (40 ml) and the MeOH was removed *in vacuo*. Work-up (EtOAc extraction, H_2O, $NaHCO_3$aq and NaClaq) afforded an oil (3·2 g) which was treated with 0·25 *M* KOH–MeOH (250 ml) at 25° under N_2 for 16 hr. Addition of AcOH (4 ml) and toluene (100 ml) and removal of MeOH *in vacuo* was followed by work-up (EtOAc extraction, H_2O, $NaHCO_3$aq and NaClaq) to give an oil (2·5 g). Chromatography of the oil on alumina (Act I, neutral: 130 g) with $CHCl_3$–EtOAc (5:1) gave a fraction (1·19 g) containing mainly the mixture of diones **19** and **20** and a second fraction (495 mg) comprising **17** and **18**. Rechromatography of the former fraction on silica gel (200 g) with $CHCl_3$-EtOAc (7:1) gave pure **19** + **20** (680 mg), which was crystallized from CH_2Cl_2-hexane to give *9-methyl-19-nor-9β,10α-progesterone* (**19**; 330 mg), m.p. 132–135°, $[\alpha]_D$ −3·5° (*c* 1·0), ν_{max} 1703, 1665 and 1615 cm^{-1}, $\Delta\epsilon$ −16·5 and +5·2 (at 242 and 290 nm resp), δ 0·71 (3H, s, 13β-Me), 0·90 (3H, s, 9β-Me), 2·12 (3H, s, 21-H_3) and 5·93 (1H, br.s, $w_{1/2}$ 5 Hz, 4-H) (Found: C, 79·9; H, 9·6; M^+, 314. $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6%; M, 314). Rechromatography of the second fraction (containing **17** and **18**) on silica gel (80 g) with $CHCl_3$-EtOAc (7:2) gave *5-hydroxy-9-methyl-19-nor-5β,9β,10α-pregnane-3,20-dione* (**17**; 320 mg), m.p. 200–208° (from EtOAc), $[\alpha]_D$ +59° (*c* 0·9), ν_{max} 3590, 3490 and 1705 cm^{-1}, $\Delta\epsilon$ +2·2 (2·83 nm), δ (C_5D_5N) 0·68 (3H, s, 13β-Me), 1·30 (3H, s, 9β-Me), 2·09 (3H, s, 21-H_3) and 4·70 (1H, s, 5-OH) (Found: C, 76·2; H, 9·6; M^+, 332. $C_{21}H_{32}O_3$ requires: C, 75·9; H, 9·7%; M, 332). Further elution with the same solvent gave *5-hydroxy-9-methyl-19-nor-5β,9β,10α,17α-pregnane-3,20-dione* (**18**; 77 mg), m.p. 220–230° (from CH_2Cl_2-hexane), $[\alpha]_D$ −110° (*c* 0·6), ν_{max} 3590, 3490 and 1705 cm^{-1}, $\Delta\epsilon$ −4·4 (283 nm), δ (C_5D_5N) 0·90 (3H, s, 13β-Me), 1·27 (3H, s, 9β-Me) and 2·12 (3H, s, 21-H_3) (Found: C, 76·2; H, 9·8%; M^+, 332).

Conversion of 17 to 19. The compound **17** (220 mg) in benzene (80 ml) under N_2 was treated with *M* TsOH–MeOH (0·4 ml) at 25° for 16 hr. Work-up (benzene extraction, aqueous $NaHCO_3$ and NaCl) gave a residue which was adsorbed on silica gel (50 g) and eluted with $CHCl_3$–EtOAc (4:1) to give **19** (183 mg) identical to that from the previous experiment.

9-Methyl-19-nor-9β,10α,17α-progesterone (**20**). Compound **18** (45 mg) was treated as described in the aforegoing experiment. Chromatography of the product on silica gel (10 g) with $CHCl_3$–EtOAc (4:1) gave **20** (37 mg) as an oil, $[\alpha]_D$ −169° (*c* 1·0), ν_{max} 1700, 1662 and 1612 cm^{-1}, $\Delta\epsilon$ −16·8, −1·7 and +2·0 [242, 281 (inflection) and 318 nm resp.], δ 0·88 (3H, s, 9β-Me), 1·00 (3H, s, 13β-Me), 2·17 (3H, s, 21-H_3) and 5·91 (1H, s, $w_{1/2}$ 5 Hz, 4-H) (Found for material distilled at 130°; $4\cdot10^{-4}$ Torr: C, 80·2; H, 9·6; M^+, 314·2241. $C_{21}H_{30}O_2$ requires: C, 80·2; H, 9·6%; M, 314·2246).

Hydrolysis and cyclization of the 17β-acetyl compound (**15**). Compound **15** (150 mg) was treated with MeOH–AcOH–H_2O as described for the hydrolysis of the mixture of **15** and **16**. The oily product was treated with 0·1 *M* KOH–MeOH (30 ml) at 25° under N_2 for 16 hr. The reaction was quenched with AcOH (0·2 ml) and worked up [extraction with EtOAc-benzene (1:1) and aqueous NaCl] to give an oil, which was adsorbed on silica gel (15 g). Elution with $CHCl_3$–EtOAc (4:1) gave **19** contaminated with **20** (*ca.* 5% by GLC: OV-101, 225°) 31 mg). Crystallization from CH_2Cl_2-hexane afforded pure **19** (26 mg) identical to that prepared previously. Further elution with the same solvent gave **17** (45 mg) and **18** (*ca.* 3 mg) identified by TLC comparison with samples described above.

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