Reconstruction of Ring A of 3,4-Dinor-2,5-seco Steroids

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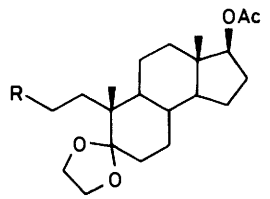
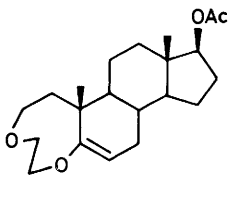
Methods for the reconversion of 3,4-dinor-2,5-seco steroids into the parent 4-en-3-one systems are discussed. In an efficient route, reaction of 17β-acetoxy-5,5-ethylenedioxy-3,4-dinor-2,5-secoandrostan-2-al with ethoxyvinyl-lithium led to the corresponding 2ξ-hydroxy-3-one. Acetylation followed by treatment with zinc dust in acetic acid then gave testosterone acetate. A similar series of reactions was performed in the progesterone series.

We have previously reported a highly efficient route for the removal of atoms C-3 and C-4 from steroidal 4-en-3-ones.[1] The 3,4-dinor-2,5-seco 2-alcohol (**1**) thus obtained has recently been utilised as the starting point for a novel synthesis of 3-thia analogues of testosterone[2] and of 4-nor-3-thia-androst-5-en-17β-ol.[3] We now report the results of work directed towards the reconversion of the dinor alcohol (**1**) into the original 4-en-3-one system. A major objective of this work was to assess the feasibility of using such methodology for the preparation of 3,4-[$^{13}C_2$]-labelled steroids.

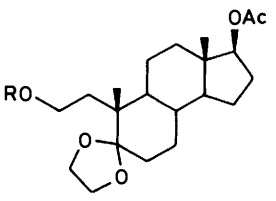
Attempts to convert the alcohol (**1**) into the halide (**2**) met with failure. The most significant product isolated from these reactions was the bis ether (**4**). The same product (**4**) was also



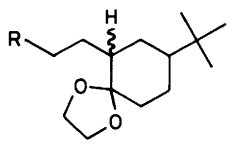
(**1**) R = OH
(**2**) R = Cl or Br
(**3**) R = C≡CH



(**4**)

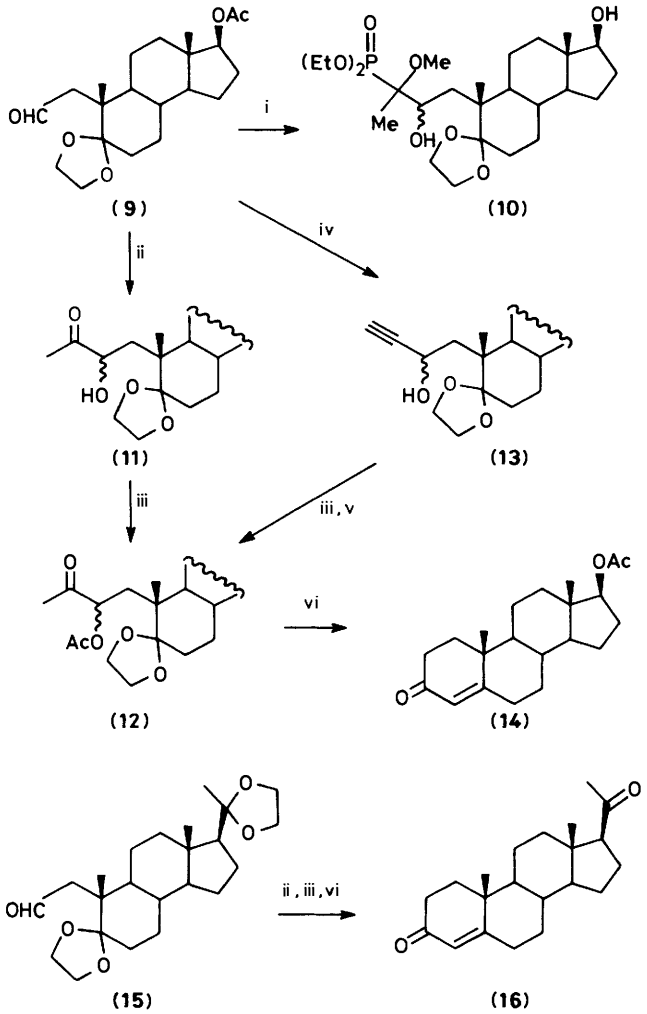


(**5**) R = SOC_6H_4Me-*p*
(**6**) R = $SO_2C_6H_4Me$-*p*



(**7**) R = $OSO_2C_6H_4Me$-*p*
(**8**) R = C≡CH

obtained from reaction of the alcohol (**1**) with toluene-*p*-sulphonyl chloride. However, treatment of the alcohol (**1**) with toluene-*p*-sulphinyl chloride gave a diastereoisomeric mixture of the 2-sulphinyloxy compounds (**5**) [δ 7.32 and 7.61 (each 2 H, d, ArH)]. Oxidation[4] of this mixture with *m*-chloroperbenzoic acid (MCPBA) afforded a rather unstable product, the n.m.r. spectrum of which [δ 7.34 and 7.82 (each 2 H, d, ArH)] was consistent with its formulation as the required toluene-*p*-sulphonate (**6**). Immediate reaction of this product with sodium acetylide in hexamethyl phosphoric triamide (HMPA), conditions which had been shown to be optimum for the conversion of the model toluene-*p*-sulphonate (**7**) into the alkyne (**8**),[5] gave, however, none of the required product (**3**). Instead, a low yield of the bis ether (**4**) was isolated.



Scheme. *Reagents:* i, LDA, $(EtO)_2P(O)CH(OMe)CH_3$; ii, $EtOCH{=}CH_2$, Bu^{t}Li; iii, Ac_2O, pyridine; iv, HC≡CLi; v, HgO, H_2SO_4; vi, Zn, HOAc

Persistent participation of the 5,5-ethylenedioxy group in the reactions of the alcohol (**1**) led us to consider the readily available‡ aldehyde (**9**) as an alternative starting point for the reconstruction of ring A. Of various Wittig–Horner reagents[6] which might have been expected to undergo condensation with

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‡ See ref. 1 and Experimental section, this paper.

the aldehyde (**9**) to give overall addition of an acetyl synthon, the most promising was diethyl (1-methoxyethyl)phosphonate. Treatment of this phosphonate with lithium di-isopropylamide (LDA) at −95 °C followed by addition of the aldehyde (**9**) led to isolation of the expected diastereoisomeric mixture of adducts (**10**) in 84% yield. We were, however, unsuccessful in our attempts to convert the adducts (**10**) into the required enol ether. Addition of ethoxyvinyl-lithium[7] to 17β-acetoxy-5,5-ethylenedioxy-3,4-dinor-2,5-secoandrostan-2-al (**9**) also proceeded smoothly. Chromatography of the reaction product on a silica gel column was accompanied by hydrolysis of the enol ether function and afforded the α-hydroxy ketone (**11**), as a mixture of epimers at C-2, in 87% yield. Acetylation and crystallisation of the product from methanol gave a single epimer of the diacetoxy ketone (**12**). The same diacetate was also obtained by an alternative route as follows. Treatment of the aldehyde (**9**) with lithium acetylide in tetrahydrofuran (THF)[8] gave the propargylic alcohols (**13**) in 75% yield. Acetylation, followed by hydration of the alkyne, then gave the diacetoxy ketone (**12**), albeit in an unoptimised yield of only 36%. Finally, reductive cleavage of the 2-acetoxy group, hydrolysis of the 5,5-ethylenedioxy group, and cyclisation of ring A were all achieved in a one-pot reaction employing zinc dust in refluxing acetic acid. Testosterone acetate (**14**) was isolated in 44% yield (Scheme). In an analogous series of reactions, 5,5;20,20-bis(ethylenedioxy)-3,4-dinor-2,5-secopregnan-2-al (**15**) was converted *via* the ethoxyvinyl-lithium adduct into progesterone (**16**).

It is thus established that 3,4-dinor-2,5-seco steroids[1] are convenient substrates for the synthesis of both heteroatom-substituted steroid analogues[2,3] and, potentially, of isotopically labelled natural steroids.

Experimental

General directions are as previously described.[1]

Reaction of 5,5-*Ethylenedioxy*-3,4-*dinor*-2,5-*secoandrostane*-2,17β-*diol* 17-*Acetate* (**1**) *with Toluene*-p-*sulphonyl Chloride*.—5,5-Ethylenedioxy-3,4-dinor-2,5-secoandrostane-2,17β-diol 17-acetate (**1**) (200 mg) was added to a solution of toluene-*p*-sulphonyl chloride (115 mg) in pyridine (4 ml) at 0 °C. After 24 h at 0 °C, the mixture was poured into water and extracted with ether. The extracts were washed successively with 2M-hydrochloric acid and water, dried, and evaporated. The residue was chromatographed on a silica gel column (eluant 25% ethyl acetate in light petroleum) to yield the *bis ether* (**4**) (57 mg), m.p. 119—121 °C (Found: C, 72.2; H, 9.8. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.7%); $\nu_{max.}$ 1 730 and 1 665 cm^{-1}; δ 0.82, 1.02, and 2.04 (each 3 H, s, 18- and 19-H_3 and OAc respectively), 3.3—4.1 (6 H, m, OCH_2CH_2O and 2-H_2), 4.65 (1 H, t, *J* 7 Hz, 17-Hα), and 5.02 (1 H, d, *J* 5 Hz, 6-H); *m/z* 348 (M^+, 100%) and 305 (43).

5,5-*Ethylenedioxy*-3,4-*dinor*-2,5-*secoandrostane*-2,17β-*diol* 17-*Acetate* 2-*Toluene*-p-*sulphinate* (**5**).—A solution of 5,5-ethylenedioxy-3,4-dinor-2,5-secoandrostane-2,17β-diol 17-acetate (**1**) (175 mg) in ether (3 ml) was added dropwise to a solution of toluene-*p*-sulphinyl chloride (98 mg) and pyridine (42 mg) in ether (2 ml) at 0 °C. The mixture was allowed to warm to room temperature and after 5 h was washed successively with 2M-hydrochloric acid, aqueous 2M-sodium carbonate, and saturated aqueous sodium chloride, dried, and evaporated. The residue was chromatographed on silica gel (eluant 20% ethyl acetate in light petroleum) to afford *S*-*p*-tolyl toluene-*p*-thiosulphonate (10 mg), m.p. 76—78 °C (lit.,[9] 76—77 °C) followed by the 2-toluene-*p*-sulphinate (**5**) (173 mg, 72%), m.p. 123—126 °C; $\nu_{max.}$ 1 740, 1 730, 1 250, and 1 130 cm^{-1}; δ 0.78, 0.97, 2.03, and 2.42 (each 3 H, s, 18- and 19-H_3, OAc, and ArCH_3 respectively), 3.6—4.3 (6 H, m, 2-H_2 and OCH_2CH_2O), 4.56 (1 H, t, *J* 7 Hz, 17-Hα), and 7.32 and 7.61 (each 2 H, d, *J* 7 Hz, ArH); *m/z* 365 (10%, M^+ − ArSO), 349 (62, M^+ − $ArSO_2$), and 99 (100).

5,5-*Ethylenedioxy*-3,4-*dinor*-2,5-*secoandrostane*-2,17β-*diol* 17-*Acetate* 2-*Toluene*-p-*sulphonate* (**6**) *and its Reaction with Sodium Acetylide*.—A solution of MCPBA (47 mg) in dichloromethane (2 ml) was added dropwise to a solution of the sulphinate ester (**5**) (100 mg) in dichloromethane (2 ml) at 0 °C. After 2.5 h at 0 °C the mixture was washed successively with aqueous 2M-potassium carbonate and water, dried, and evaporated under reduced pressure at 0 °C to yield the toluene-*p*-sulphonate (**6**) as an oily residue (70 mg, 73%); $\nu_{max.}$ 1 730, 1 360, 1 190, and 1 175 cm^{-1}; δ 0.78, 0.97, 2.03, and 2.45 (each 3 H, s, 18- and 19-H_3, OAc, and ArCH_3 respectively), 3.8 (4 H, br s, OCH_2CH_2O), 3.9—4.3 (2 H, m, 2-H_2), 4.57 (1 H, t, *J* 7 Hz, 17-Hα), and 7.34 and 7.82 (each 2 H, d, *J* 7 Hz, ArH). This material was used directly for the following experiment.

Acetylene was bubbled through anhydrous liquid ammonia at −70 °C for 5 min. Sodium (0.5 g) was added. After 10 min, the passage of acetylene was stopped, the cooling bath was removed, and the ammonia was evaporated off by gentle warming under nitrogen. The residue was dissolved in HMPA (5 ml) and then the solution was saturated with acetylene at room temperature. A solution of the aforementioned toluene-*p*-sulphonate (70 mg) in HMPA (2 ml) was added dropwise to this solution. After 2 h the mixture was poured onto ice and extracted with hexane. Careful t.l.c. examination of the reacetylated product thus obtained showed that it contained none of the required alkyne (**3**).[5] The only characterised product was the bis ether (**4**).

17β-*Acetoxy*-5,5-*ethylenedioxy*-3,4-*dinor*-2,5-*secoandrostan*-2-*al* (**9**).—A solution of 5,5-ethylenedioxy-3,4-dinor-2,5-secoandrostane-2,17β-diol 17-acetate (**1**) (400 mg) in dichloromethane (5 ml) was added to a suspension of pyridinium chlorochromate (529 mg) and anhydrous sodium acetate (500 mg) in dichloromethane (10 ml). After the mixture had been stirred for 2 h, ether (50 ml) was added and the supernatant liquid was decanted. The insoluble residue was washed thoroughly with ether. The combined ether layers were passed through a short column of silica gel. Evaporation of the eluant gave the required 2-aldehyde (**9**) (330 mg, 83%), m.p. 153—156 °C (lit.,[1] 153—156 °C).

Similar oxidation of 5,5;20,20-bis(ethylenedioxy)-3,4-dinor-2,5-secopregnan-2-ol[1] afforded the corresponding *aldehyde* (**15**) (60%), m.p. (from ethyl acetate–hexane) 175—177 °C (Found: C, 70.4; H, 9.4. $C_{26}H_{36}O_5$ requires C, 70.4; H, 9.2%); $\nu_{max.}$ 1 710 cm^{-1}; δ 0.76, 1.17, and 1.26 (each 3 H, s, 18-, 19-, and 21-H_3 respectively), 3.65—4.00 (8 H, m, 2 × OCH_2CH_2O), and 9.70 (1 H, t, *J* 4 Hz, 2-H).

Diethyl (1-*Methoxyethyl*)*phosphonate*.—α-Chloroethyl methyl ether[10] (25 g) and triethyl phosphite (40 g) were heated under reflux for 4.5 h. Vacuum distillation gave the title phosphonate (25.5 g, 49%), b.p. 73—75 °C at 0.8 mmHg; $\nu_{max.}$ (neat) 1 238 and 1 025 cm^{-1}; δ 1.34 (6 H, t, *J* 7 Hz), 1.48 (3 H, d, *J* 7 Hz), 3.50 (3 H, s), 3.60 (1 H, q, *J* 7 Hz), and 4.18 (4 H, q, *J* 7 Hz); *m/z* 184 (100%) and 59 (29).

Reaction of the 2-*Aldehyde* (**9**) *with Diethyl* (1-*Methoxyethyl*)-*phosphonate*.—A solution of di-isopropylamine (0.74 ml) in THF (10 ml) was cooled to −78 °C and n-butyl-lithium (3.4 ml; 1.55M solution in hexane) was added. A solution of freshly distilled diethyl (1-methoxyethyl)phosphonate (0.9 g) in THF (2 ml) was then added during 5 min and the mixture was then cooled to −100 °C. To this mixture was added a solution of 17β-acetoxy-5,5-ethylenedioxy-3,4-dinor-2,5-secoandrostan-2-al (**9**) (340 mg) in THF (3 ml) dropwise during 20 min. After a further

15 min at −100 °C, the mixture was allowed to warm to room temperature and was then poured into ether. The solution was washed successively with aqueous 50% citric acid, water, and 2M-sodium carbonate, dried, and evaporated. Chromatography of the residue on silica gel with 20% ethanol in ether as eluant gave a mixture of the diastereoisomeric adducts (**10**) as a gum (410 mg, 84%); $\nu_{max.}$ (neat) 3 400, 1 220, and 1 030 cm^{-1}; δ 0.75 and 0.80 (total 3 H, s, 18-H_3), 1.08 and 1.13 (total 3 H, s, 19-H_3), 3.40 and 3.47 (total 3 H, s, OMe), 3.98 (4 H, br s, OCH_2CH_2O), and 3.90—4.40 (4 H, m, 2 × OCH_2). Attempts to cleave this material to give the corresponding enol ether by pyrolysis or by using potassium t-butoxide or potassium hydride were not successful.

Reaction of the 2-*Aldehyde* (**9**) *with Ethoxyvinyl-lithium.*—A solution of ethyl vinyl ether (450 mg) in THF (10 ml) was cooled under nitrogen to −78 °C and t-butyl-lithium (2.6 ml; 1.4M-solution in pentane) was added. As the mixture warmed, the yellow precipitate redissolved to give a colourless solution by 0 °C. The solution was cooled to −95 °C and a solution of the 2-aldehyde (**9**) (230 mg) in THF (4 ml) was added during 10 min. The mixture was allowed to warm to room temperature, aqueous 20% ammonium chloride was added, and the mixture was extracted with ether. The combined extracts were washed with water, dried, and evaporated to leave an oil ($\nu_{max.}$ 3 430, 1 665, and 1 620 cm^{-1}) which, upon chromatography on silica gel with 60% ethyl acetate in light petroleum as eluant, gave 5,5-ethylenedioxy-2,17β-dihydroxy-4,5-secoandrostan-3-one (200 mg, 87%); $\nu_{max.}$ 3 400 and 1 710 cm^{-1}. Acetylation with acetic anhydride in pyridine at room temperature gave the corresponding diacetate (**12**) (195 mg, 81%) as a mixture of epimers at C-2. Crystallisation from methanol afforded a pure single epimer of 2ξ,17β-*diacetoxy*-5,5-*ethylenedioxy*-4,5-*secoandrostan*-3-*one* (**12**), m.p. 138—141 °C (Found: C, 66.55; H, 8.5. $C_{25}H_{38}O_7$ requires C, 66.6; H, 8.5%); δ (200 MHz) 0.80 (3 H, s, 18-H_3), 1.12 (3 H, s, 19-H_3), 2.04 (3 H, s, 17-OAc), 2.12 and 2.13 (total 6 H, each s, 2-OAc and 4-H_3), 3.9—4.1 (4 H, m, OCH_2CH_2O), 4.56 (1 H, m, 17-Hα), and 5.40 (1 H, dd, *J* 2 and 8 Hz, 2-H); *m/z* 450 (M^+, 4%) and 99 (100).

Similarly, 5,5;20,20-bis(ethylenedioxy)-3,4-dinor-2,5-secopregnan-2-al (**15**) gave 2-acetoxy-5,5;20,20-bis(ethylenedioxy)-4,5-secopregnan-3-one (66%) as a mixture of isomers at C-2; δ 0.78 (3 H, s, 18-H_3), 0.96 and 1.03 (total 3 H, each s, 19-H_3), 1.28 (6 H, s, 4- and 21-H_3), 2.02 (3 H, s, OAc), 3.80—4.10 (8 H, m, 2 × OCH_2CH_2O), and 5.62 (1 H, m, 2-H).

Alternative Preparation of 2,17β-*Diacetoxy*-5,5-*ethylenedioxy*-4,5-*secoandrostan*-3-*one* (**12**).—Acetylene was bubbled into THF (7 ml) cooled to −78 °C. n-Butyl-lithium (2.4 ml; 1.5M-solution in hexane) was then added dropwise. After 5 min, the mixture was cooled to −98 °C, the flow of acetylene was stopped, and a solution of 17β-acetoxy-5,5-ethylenedioxy-3,4-dinor-2,5-secoandrostan-2-al (**9**) (200 mg) in THF (2 ml) was added dropwise. The mixture was stirred at −98 °C for 20 min, and then allowed to warm to room temperature. Water (15 ml) was added followed by solid potassium carbonate until the aqueous phase became pasty. The mixture was then extracted with ether. The combined extracts were washed with water, dried, and evaporated. Chromatography of the residue on a silica gel column with 40% ethyl acetate in light petroleum as eluant gave 5,5-ethylenedioxy-4,5-secoandrost-3-yne-2ξ,17β-diol 17-acetate (**13**) (160 mg, 75%); $\nu_{max.}$ 3 450, 3 300, and 1 730 cm^{-1}; *m/z* 390 (M^+, 1%) and 328 (100). Treatment with acetic anhydride in pyridine at room temperature gave the corresponding 2,17-diacetate (152 mg, 82%); δ 0.82 and 1.07 (each 3 H, s, 18- and 19-H_3), 2.04 and 2.06 (each 3 H, s, 2 × OAc), 2.42 (1 H, d, *J* 2 Hz, 4-H), 4.0 (4 H, br s, OCH_2CH_2O), 4.60 (1 H, t, *J* 7 Hz, 17-Hα), and 5.85 (1 H, m, 2-H); *m/z* 432 (M^+, 2%) and 99 (100).

Yellow mercury(II) oxide (650 mg) was stirred with water (5 ml) and conc. sulphuric acid (0.8 ml). A solution of 5,5-ethylenedioxy-4,5-secoandrost-3-yne-2ξ,17β-diol diacetate (50 mg) in dioxane (1 ml) was added to the mercury oxide solution (2 ml) and the mixture was stirred for 2.5 h before being extracted with chloroform. The extracts were washed with water, dried, and evaporated to give a mixture of the C-2 epimers of 2,17β-diacetoxy-5,5-ethylenedioxy-4,5-secoandrostan-3-one (**12**) (19 mg, 36%), identical with material prepared as above.

Treatment of 2ξ,17β-*Diacetoxy*-5,5-*ethylenedioxy*-4,5-*secoandrostan*-3-*one* (**12**) *with Zinc Dust.*—The title compound (100 mg) and zinc dust (300 mg) were refluxed in glacial acetic acid (5 ml) for 12 h. The zinc dust was filtered off and washed thoroughly with ether. The combined organic layers were washed successively with 2M-sodium hydrogen carbonate and water, then dried and evaporated. The residue was separated by preparative layer chromatography (developer 30% ethyl acetate in light petroleum) to give testosterone acetate (**14**) (32 mg, 44%), m.p. 138—141 °C, identical in all respects with an authentic sample, and 17β-acetoxy-4,5-secoandrostane-3,5-dione (12 mg); δ 0.80, 1.06, 1.98, and 2.10 (each 3 H, s, 18- and 19-H_3, OAc, and 4-H_3 respectively) and 4.58 (1 H, t, *J* 7 Hz, 17-Hα); *m/z* 348 (M^+, 1%), 330 (100), and 278 (98).

Similar reduction of 2ξ-acetoxy-5,5;20,20-bis(ethylenedioxy)-4,5-secopregnan-3-one (60 mg) with zinc dust (200 mg) for 15 h yielded progesterone (**16**) (14 mg, 35%), m.p. 128—130 °C, identical in all respects with an authentic sample.

Acknowledgements

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References

1 R. B. Boar, S. L. Jones, and A. C. Patel, *J. Chem. Soc., Perkin Trans. 1*, 1982, 513.
2 G. A. Flynn, *J. Org. Chem.*, 1983, **48**, 4125.
3 G. A. Flynn, *Synth. Commun.*, 1984, **14**, 301.
4 R. M. Coates and J. P. Chen, *Tetrahedron Lett.*, 1967, 2705.
5 A. C. Patel, Ph.D. Thesis, University of London, 1983.
6 See, for example, S. Warren, *Chem. Ind. (London)*, 1980, 824; A. F. Kluge and J. S. Cloudsdale, *J. Org. Chem.*, 1979, **44**, 4847.
7 J. E. Baldwin, G. A. Hofle, and O. W. Lever, *J. Am. Chem. Soc.*, 1974, **96**, 7125.
8 M. M. Midland, *J. Org. Chem.*, 1975, **40**, 2250.
9 M. Furukawa, T. Okawara, Y. Noguchi, and M. Nishikawa, *Synthesis*, 1978, 441.
10 H. R. Henze and J. T. Murchison, *J. Am. Chem. Soc.*, 1931, **53**, 4077.

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