Direct Conversion of 13β-Alkylgonatetraenes into 13β-Alkylgon-4-en-3-ones

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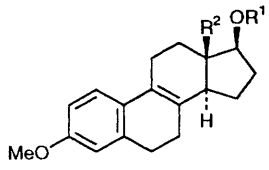
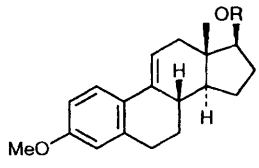
Birch reduction of 8,9-didehydroestradiol-17β 3-methyl ether **1** or 9(11)-didehydroestradiol-17β 3-methyl ether **2** followed by acid hydrolysis results in a mixture of 19-nortestosterone **8** and 19-nor-9β,10α-testosterone **9** in varying amounts. However, reduction of their acetates with sodium or lithium, *tert*-butyl alcohol in liquid ammonia and in the presence of aniline affords exclusively 19-nortestosterone. Similarly, 18a-homo-19-nortestosterone **12** is prepared from the acetate of 18a-homoestradiol-17β 3-methyl ether, **10**.

The conversion of estradiol into 19-nortestosterone **8**, the first synthetic progestogen of considerable biological interest, was reported by Birch.[1] In view of the importance of 19-norsteroids as oral contraceptives,[2] total synthesis of estrone and other aromatic steroids has been the target for many years. This was successfully accomplished by Torgov[3] and Smith[4] and the method is now viable for commercial production of estrone and its analogues.

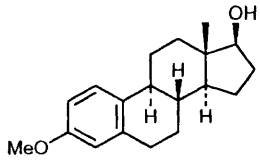
In the Torgov–Smith synthesis, the 8,9-didehydroestradiol-17β 3-methyl ether **1** is reduced with potassium in liquid ammonia in the presence of aniline to yield the estradiol 3-methyl ether **3**. This is further subjected[5] to Birch reduction in the presence of a proton donor to give the dihydro compound **5**, which is converted into 19-nortestosterone **8** on acid hydrolysis. Although metal–ammonia reduction of styrenoid compounds usually produces[6] the most stable products, difficulties were encountered in the reduction of compound **1**, leading to a mixture of isomeric estradiol ethers **3** and **4**. However, this difficulty was circumvented by first isomerizing the 8(9)-double bond in compound **1** to the more stable 9(11)-position to afford compound **2**, which was then catalytically hydrogenated to yield exclusively the estradiol 3-methyl ether **3**. Although direct metal–ammonia reduction of 8,9-didehydroestradiol-17β 3-methyl ether **1** in the presence of a proton source, followed by acid hydrolysis, should result in the formation of 19-nortestosterone, this could not be accomplished due to the formation of a mixture of 19-nortestosterone **8** and 19-nor-9β,10α-testosterone **9**. We have earlier investigated[7] the reduction of several styrenoid compounds including isomers **1** and **2** with metal–ammonia solutions and isolated a mixture of isomeric compounds. There have been many instances[8–12] in the literature wherein isomeric products were formed during metal–ammonia reduction of styrenoid compounds. Further, differences in the yield and isomeric ratio of the products were also reported in the literature, when different alkali metals were employed in the Birch reduction.[8,13] Therefore we reinvestigated the metal–ammonia reductions of isomers **1** and **2** by employing lithium, sodium and potassium, and found that the isomeric ratios of the products were unaltered, indicating that the nature of the cation is unimportant and also indicating the involvement of solvent-separated ion-pairs rather than tight-ion-pairs. We have postulated[14] that the mechanism of reduction of styrenes with metal–ammonia solutions involves the protonation of intermediate anion radicals, rather than dianions, to account for the formation of stereoisomeric products.



1 R^1 = H, R^2 = Me
6 R^1 = Ac, R^2 = Me
10 R^1 = Ac, R^2 = Et



2 R = H
7 R = Ac



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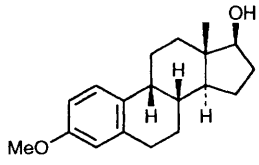

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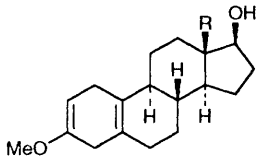
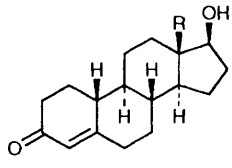
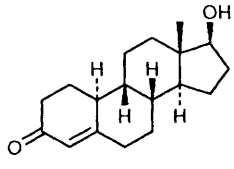


5 R = Me
11 R = Et



8 R = Me
12 R = Et



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Results and Discussion

We now report a simple and convenient method for the direct conversion of compounds **1**, **2** and **10** into the corresponding 19-nortestosterone derivatives through their acetates. Use of aniline has been prevalent in Birch reduction of styrene systems, since it plays various roles in these reductions. Use of ethylaniline is found not to give dimerization of 1,1-diphenylaniline under metal–ammonia conditions.[15] Aniline is known to accelerate the reductions of diphenylethene and diphenylacetylene.[16] Usage of aniline to change the isomeric ratios of the products in the styrene reductions have also been documented.[17] Birch reduction of compound **1** with sodium in

liquid ammonia and in the absence of an external proton donor resulted in a mixture of isomeric estradiol derivatives **3** and **4** in 2:1 ratio while reduction of compound **1** in the presence of aniline yielded exclusively the product of natural stereochemistry **3**. Hence direct reduction of compound **1** with Na/liq. NH_3 and in the presence of aniline and Bu^{t}OH was attempted. The product was hydrolysed to yield 19-nortestosterone **8** as the major product in 65% yield. A small amount (5%) of 19-nor-9β,10α-testosterone **9** was also isolated. Similar results were obtained when employing lithium. Since Birch reduction of compound **1** yielded a mixture, reduction of its acetate **6** was examined. Acetylation of compound **1** with acetic anhydride and pyridine afforded the acetate **6**, which was reduced with sodium or lithium and *tert*-butyl alcohol in liquid ammonia, followed by acid hydrolysis to give a mixture of isomers **8** and **9** in 70:30 ratio. Similarly, reduction of the acetate **7**, prepared from compound **2**, with sodium/lithium in liquid ammonia and in the presence of *tert*-butyl alcohol gave the tetrahydro compound which was hydrolysed to 19-nortestosterone **8** and 19-nor-9β,10α-testosterone **9**. On the other hand, reduction of the acetates **6** and **7** with Na or Li/aniline/Bu^{t}OH in liquid ammonia, followed by acid hydrolysis, afforded exclusively 19-nortestosterone **8** in 70% yield. Similar reduction of the acetate **10** with sodium or lithium and *tert*-butyl alcohol in liquid ammonia and in the presence of aniline afforded the tetrahydro compound **11**, which was hydrolysed to the 18a-homo-19-nortestosterone **12** in 68% yield. The structures of all the compounds were established from spectral data and comparison with authentic samples. In the case of the mixtures of estradiol methyl ethers **3** and **4**, and their oxidation products estrone methyl ether and 9β-estrone methyl ether, the presence or absence of a mixture of isomers was checked by ^{1}H NMR and ^{13}C NMR spectroscopy, since they do not separate either in column chromatography or in HPLC. In the case of the 19-nor series the isomers are separable by column chromatography and the absence of the minor stereoisomer was confirmed by ^{13}C NMR spectroscopy.

In conclusion the present method offers a convenient, one-step, direct route to 19-norsteroids from the corresponding 8,9- or 9,11-didehydroestratetraenes. This method will also have an impact on the industrial production of 19-norsteroids, since it avoids the isomerization and hydrogenation steps.

Experimental

M.p.s were determined on a Metler FP1 apparatus and are uncorrected. IR spectra were recorded for liquid films or Nujol mulls on a Perkin-Elmer Model-781 instrument. NMR spectra were recorded on a JEOL FX 90Q spectrometer. Chemical shifts are given in ppm (δ) downfield from tetramethylsilane as internal standard with the usual abbreviations. *J* Values are given in Hz. Mass spectra were recorded on a JEOL MS-DX 303 spectrometer with a built-in inlet system. Analytical TLC was carried out on glass plates with silica gel (0.2 mm, commercial grade containing 10% calcium sulfate binder) activated at 70–90 °C for 1 h prior to use. Liquid ammonia was distilled from sodium amide. Extracts were dried over anhydrous Na_2SO_4.

Reduction of 8,9-*Didehydroestradiol* 3-*Methyl Ether* **1**.—(i) *With Lithium*. The 8,9-didehydroestradiol methyl ether **1** (0.284 g, 1 mmol) was added in dry tetrahydrofuran (THF) (5 cm^3) to distilled liquid ammonia (50 cm^3). Lithium (0.028 g, 0.004 mol) was added and the resulting blue complex was stirred for 30 min; then ammonium chloride was added to quench the reaction, ammonia was allowed to evaporate off, and the product was extracted in diethyl ether. After the usual work-up, the crude gummy product was dissolved in acetone (10 cm^3) and the solution was cooled to 0 °C. A slight excess of Jones reagent was added, the mixture was stirred for 4 h and worked up as usual, and the product was purified by silica gel column chromatography to yield a mixture of isomeric estrone methyl ethers (71%), δ_H 0.9 (3 H, s, Me integrating to 33%), 0.98 (3 H, s, Me integrating to 66%), 1–3 (13 H, m), 3.7 (3 H, s, OMe) and 6.5–7.1 (3 H, m, ArH).

The two isomers could be separated by trituration of the product mixture with methanol. The *trans* isomer, estrone methyl ether, was precipitated and recrystallized from methanol; m.p. 141.5 °C (lit.,[4] 143–144 °C). The mother liquor, on concentration followed by preparative TLC and crystallization from methanol, gave the 9β-estrone methyl ether; m.p. 66.4 °C (lit.,[4] 67–68 °C).

(ii) *With sodium*. Reduction of compound **1** (1 mmol) with sodium (0.004 mol) following the procedure given above, and subsequent oxidation with Jones reagent, gave a mixture of 9α- and 9β-estrone methyl ethers in 2:1 ratio.

(iii) *With potassium*. Reduction of compound **1** (1 mmol) with potassium (0.004 mol), followed by Jones oxidation as described above, gave 9α- and 9β-estrone methyl ethers in 2:1 ratio.

(iv) *In the presence of aniline*. 8,9-Didehydroestrone 3-methyl ether **1** (0.284 g, 1 mmol) as a solution in dry THF (5 cm^3) was added to distilled liquid ammonia (50 cm^3), lithium (0.028 g, 0.004 mol) and distilled aniline (1 cm^3) were added, and the mixture was stirred for 30 min after which it was quenched with NH_4Cl. The product was extracted with diethyl ether, and the extract was washed well with 5 mol dm^{-3} HCl and then with water, then dried, and the solvent was removed. The crude product was dissolved in acetone and Jones reagent was added at 0 °C. After the usual work-up the oxidized product was purified by silica gel column chromatography to yield estrone methyl ether (75%).

3-*Methoxy*-13β-*methylgona*-1,3,5(10),8-*tetraen*-17β-*yl Acetate* **6**.—To an ice-cold solution of alcohol **1** (1.42 g) in pyridine (15 cm^3) was added acetic anhydride (1 cm^3) and the mixture was stirred for 12 h before being treated with 5 mol dm^{-3} HCl to neutralize pyridine and extracted with diethyl ether (3 × 50 cm^3). The extract was washed successively with water, saturated aq. sodium hydrogen carbonate, water and brine, and was dried over anhydrous sodium sulfate. Diethyl ether was removed by distillation and the crude product was purified by column chromatography to give the *acetate* **6** (1.46 g, 90%), m.p. 118.6 °C (Found: M$^+$, 326.1910. $C_{21}H_{26}O_3$ requires *M*, 326.1882); ν_{max}(Nujol)/cm^{-1} 1737 and 1611; δ_H 0.83 (3 H, s, Me), 1.42–2.9 (13 H, m), 2.08 (3 H, s, OAc), 3.8 (3 H, s, OMe), 4.76 (1 H, dd, *J* 9 and 6.3, C*H*OAc) and 6.6–7.2 (3 H, m, ArH); δ_C 11.7 (q), 21.0 (q), 22.7 (t), 24.0 (t), 24.7 (t), 28.2 (t), 28.5 (t), 33.8 (t), 42.4 (s), 46.7 (d), 55.0 (q), 81.5 (d), 110.6 (d), 113.4 (d), 122.8 (d), 125.3 (s), 129.0 (s), 131.5 (s), 137.0 (s), 157.8 (s) and 171.2 (s).

3-*Methoxy*-13β-*methylgona*-1,3,5(10),9(11)-*tetraen*-17β-*yl Acetate* **7**.—Alcohol **2** was acetylated as described above to give the acetate **7** (95%), m.p. 91.8 °C (Found: M$^+$, 326.1890%); ν_{max}(Nujol)/cm^{-1} 1731 and 1608; δ_H 0.84 (3 H, s, Me), 1.16–3.0 (12 H, m), 2.08 (3 H, s, OAc), 3.78 (3 H, s, OMe), 4.6–4.88 (1 H, m, C*H*OAc), 5.96–6.16 (1 H, m, =CH) and 6.52–7.6 (3 H, m, ArH); δ_C 11.9 (q), 20.9 (q), 24.0 (t), 27.4 (t), 28.1 (t), 29.9 (t), 38.5 (d), 39.1 (t), 41.2 (s), 47.0 (d), 54.9 (q), 82.6 (d), 112.5 (d), 113.1 (d), 117.1 (d), 125.0 (d), 127.1 (s), 134.6 (s), 137.2 (s), 158.2 (s) and 170.8 (s).

13β-*Ethyl*-3-*methoxygona*-1,3,5(10),8-*tetraen*-17β-*yl Acetate* **10**.—13β-Ethyl-3-methoxygona-1,3,5(10),8-tetraen-17β-ol was acetylated as described above to give the acetate **11** (88%), m.p. 81.5 °C (Found: M$^+$, 340.2008. $C_{22}H_{28}O_3$ requires *M*,

340.2039); ν_{max}(Nujol)/cm^{-1} 1737 and 1608; δ_H 1.0 (3 H, t, *J* 7.2, Me), 1.2–2.9 (15 H, m), 2.08 (3 H, s, OAc), 3.8 (3 H, s, OMe), 4.83 (1 H, dd, *J* 9 and 7.2, C*H*OAc) and 6.5–7.2 (3 H, m, ArH); δ_C 10.0 (q), 18.4 (t), 21.1 (q), 22.1 (t), 24.2 (t), 24.7 (t), 28.3 (t), 28.5 (t), 30.1 (t), 44.0 (s), 48.2 (d), 55.2 (q), 82.8 (d), 110.6 (d), 113.6 (d), 122.8 (d), 126.1 (s), 128.8 (s), 131.3 (s), 136.9 (s), 157.8 (s) and 171.1 (s).

General Procedure for Direct Metal–Ammonia Reduction.—*Method A*. A mixture of the substrate (1 mmol) in THF (5 cm^3) and *tert*-butyl alcohol (5 cm^3) was added to a rapidly stirred mixture of sodium or lithium (0.008 mol) in liquid ammonia (100 cm^3). The mixture was stirred for 3 h after which ammonium chloride was added to discharge the blue colour, and ammonia was allowed to evaporate off. Water (100 cm^3) was then cautiously added to the residue and the resulting mixture was extracted with diethyl ether (3 × 50 cm^3). The extract was thoroughly washed successively with water and brine, dried over anhydrous sodium sulfate, and evaporated to give the dihydro compound (90%), which showed characteristic IR absorptions bands at 1700 and 1670 cm^{-1}.

Method B. To a stirred solution of sodium (1.84 g, 0.008 mol) in liquid ammonia (100 cm^3) was added the substrate (1 mmol) in dry THF (5 cm^3) and aniline (1 cm^3). After 15 min, Bu^{t}OH (5 cm^3) was added very slowly (5 min). The mixture was stirred for 3 h and the reaction mixture was worked up as above to yield the dihydro compound.

Method C. This is essentially the same as described under method B except that lithium was used instead of sodium.

Hydrolysis of Dihydro Compounds.—To a solution of the dihydro compound (1 mmol) in methanol (50 cm^3) was added conc. HCl (5 cm^3) and the reaction mixture was refluxed for 2 h. After the mixture had cooled, saturated aq. sodium hydrogen carbonate was added to neutralize the acid and methanol was removed by distillation. To the residue was added water (80 cm^3) and the mixture was extracted with diethyl ether (3 × 30 cm^3). The extract was washed successively with water and brine and was dried over anhydrous sodium sulfate. Removal of the solvent resulted in a crude product, which was purified by column chromatography, and recrystallized from methanol to give the pure 19-nor compound.

Reduction of 8,9-*Didehydroestradiol*-17β 3-*Methyl Ether* **1**.—Reduction of compound **1** as per method A and hydrolysis of the resultant tetrahydro compound according to the above procedue gave the isomeric enones **8** (50%) and **9** (20%).

19-*Nortestosterone* **8**: m.p. 110.3 °C (lit.,[1] 111 °C); ν_{max}(Nujol)/cm^{-1} 3400, 1662 and 1616; δ_H(90 MHz; $CDCl_3$) 0.81 (3 H, s, Me), 0.84–2.6 (21 H, m), 3.66 (1 H, t, *J* 8.1, C*H*OH) and 5.82 (1 H, s, =CH).

19-*Nor*-9β,10α-*testosterone* **9**: m.p. 188 °C (lit.,[18] 188–190 °C); ν_{max}(Nujol)/cm^{-1} 3400, 1662 and 1617; δ_H(90 MHz; $CDCl_3$) 0.85 (3 H, s, Me), 1.0–2.8 (21 H, m), 3.74 (1 H, t, *J* 8.1, C*H*OH) and 5.85 (1 H, s, =CH).

Reduction of 8,9-*Didehydroestradiol*-17β 3-*Methyl Ether* **1** *in the Presence of Aniline*.—Reduction of compound **1** as per method C and hydrolysis of the resultant tetrahydro compound according to the above procedure gave the isomeric enones **8** (65%) and **9** (5%).

Reduction of 3-*Methoxy*-13β-*methylgona*-1,3,5(10),8-*tetraen*-17β-*yl Acetate* **6**.—Reduction of compound **6** as per method A gave the tetrahydro compound **5**, which was hydrolysed according to the above procedure to yield two isomeric compounds **8** (50%) and **9** (20%).

Reduction of 3-*Methoxy*-13β-*methylgona*-1,3,5(10),8-*tetraen*-17β-*yl Acetate* **6** *in the Presence of Aniline*.—Reduction of compound **6** as per method B or C gave the tetrahydro compound **5** (95%), which was hydrolysed according to the above procedure to yield 19-nortestosterone **8** (70%).

Reduction of 3-*Methoxy*-13β-*methylgona*-1,3,5(10),9(11)-*tetraen*-17β-*yl Acetate* **7** *in the Presence of Aniline*.—Reduction of compound **7** as per method B or C and hydrolysis as above yielded 19-nortestosterone **8** (70%).

Reduction of 13β-*Ethyl*-3-*methoxygona*-1,3,5(10),8-*tetraen*-17β-*yl Acetate* **11**.—Reduction of compound **10** as per method B or C gave the tetrahydro compound **11** (95%), which was hydrolysed according to the above procedure to yield 13β-ethyl-17-hydroxygon-4-en-3-one **12** (68%), m.p. 148.4 °C (lit.,[19] 149.5–150 °C); ν_{max}(Nujol)/cm^{-1} 3424, 1668 and 1623; δ_H(90 MHz; $CDCl_3$) 1.01 (3 H, t, *J* 7.5, Me), 0.72–2.7 (23 H, m), 3.75 (1 H, t, *J* 8.1, C*H*OH) and 5.83 (1 H, s, =CH).

Acknowledgements

P. B. thanks CSIR, New Delhi for the award of a research fellowship.

References

1 A. J. Birch, *J. Chem. Soc.*, 1950, 367.
2 C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sandheimer, *J. Am. Chem. Soc.*, 1954, **76**, 4092.
3 S. N. Anachenko, V. Ye Limanov, V. N. Leonov, V. M. Rzheznikov and I. V. Torgov, *Tetrahedron*, 1962, **18**, 1355.
4 G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddal and H. Smith, *J. Chem. Soc.*, 1963, 5072.
5 H. L. Dryden, Jr., G. M. Webber, R. R. Burtner and J. H. Cella, *J. Org. Chem.*, 1961, **26**, 3237.
6 W. S. Johnson, J. Ackerman, J. F. Eastman and H. A. Dewalt, Jr., *J. Am. Chem. Soc.*, 1956, **78**, 6303.
7 G. S. R. Subba Rao, N. Shyama Sundar and Uma Ramachandran, unpublished work.
8 W. S. Johnson, J. Ackerman, J. F. Eastham and H. A. DeWalt, Jr., *J. Am. Chem. Soc.*, 1956, **78**, 6302.
9 W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta, *J. Am. Chem. Soc.*, 1960, **82**, 614.
10 J. E. Cole, Jr., W. S. Johnson, P. A. Robins and J. Walker, *J. Chem. Soc.*, 1962, 244.
11 W. Nagata, T. Teraswa, S. Hirai and K. Takeda, *Tetrahedron Lett.*, 1960, 27.
12 W. Nagata, T. Terasawa, S. Hirai and K. Takeda, *Chem. Pharm. Bull.*, 1961, **9**, 709.
13 G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, *J. Am. Chem. Soc.*, 1954, **76**, 1715.
14 Uma Sheriff, Ph. D thesis, Indian Institute of Science, 1983.
15 K. Ziegler and O. Schafer, *Justus Liebigs Ann. Chem.*, 1930, **479**, 150; W. Schlenk and E. Bergmann, *Justus Liebigs Ann. Chem.*, 1930, 78; K. Ziegler, H. Colonius and O. Schafer, *Justus Liebigs Ann. Chem.*, 1929, **473**, 36.
16 S. G. Strel'tsova and E. A. Shilov, *Ukr. Khim. Zh.* (*Russ. Ed.*), 1956, **22**, 489 (*Chem. Abstr.*, 1957, **51**, 4330d).
17 G. S. R. Subba Rao and N. Shyama Sundar, *Indian J. Chem., Sect. B*, 1977, **15**, 585.
18 J. M. H. Graves, G. A. Hughes, T. Y. Jen and H. Smith, *J. Chem. Soc.*, 1964, 5488.
19 H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wendt, G. C. Buzby, Jr., R. A. Edgren, J. Fisher, T. Foell, B. Gadsby, D. Hartley, D. Herbst, A. B. A. Jansen, K. Ledig, B. J. McLoughlin, J. McMenamin, T. W. Pattison, P. C. Philips, R. Rees, J. Siddall, J. Siuda, L. L. Smith, J. Tokolics and D. H. P. Watson, *J. Chem. Soc.*, 1964, 4472.

Paper 4/00913D
Received 15*th February* 1994
Accepted 8*th April* 1994