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Application of the thermal dehydration of benzylic alcohols in the preparation of estra-1,3,5(10),6-tetraen-3,17-diol derivatives

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Introduction. The interest in radiopharmacy in estrogens as radiodiagnostic agents for estrogen dependent cancer[1] and possibly as therapeutic compounds[2] led us to prepare estradiol derivatives for subsequent radiolabeling. C-7 substituted estranes are of special importance in this respect due to their good binding affinity to the estrogen receptor ERα.[3] Similar compounds have already been prepared by us, where the 3-phenolic hydroxyl function in ring *A* is still protected as a methoxy group.[4] As the circulating estrogens in the blood stream very often possess a free 3-hydroxyl in the A-ring, the purpose of this work was to develop estradiol derivatives with an unprotected 3-

hydroxyl group and a C6,C7-olefinic bond in the *B*-ring. The additional unsaturation within the steroidal framework alters the conformation of the *B*-ring and its influence will be subject of further studies.

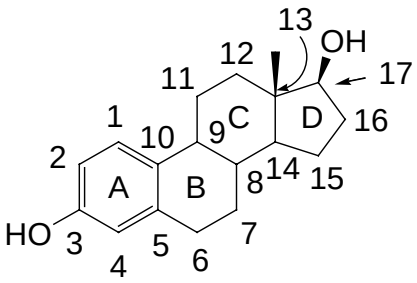
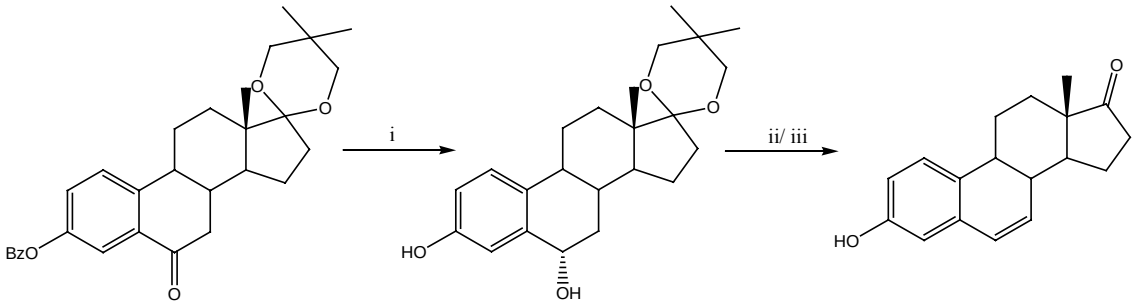


Figure 1 Estradiol

Introducing the C-7 substituent to the molecule is achieved by activation via a keto group at C6. The olefinic bond at C6/C7 is introduced by dehydration of the 6-hydroxy function, which is obtained by simple reduction of the 6-keto group. What seems to be a simple matter, poses some problems as acid catalysed dehydration does not lead to success in the case of 3-OH unprotected estradiol derivatives, as described below. In the following different methods of introduction of the C6/C7 unsaturation in estradiol derivatives will be discussed.

Results and Discussion. For the study, two compounds were prepared, estra-1,3,5(10),6-tetraene-3-ol-17-one (**3**) and the 7-substituted derivative (**6**). In both cases estrone was used as starting material. The transformations within the ring are the benzylic oxidation at C6 and the subsequent reduction of the 6-keto group. For the oxidation of the C6 position it is advisable to protect the OH function at C3; for a

subsequent reduction of C6-keto it is necessary to protect the C17 keto group. First, the OH group at C3 is protected. Here, it is important to choose a protective group that can be deprotected at a later stage under mild conditions. At first the benzoyl group was chosen and estrone benzoate was prepared[5] (quantitative yield), followed by acetalisation of 3-benzoate-estra-1,3,5(10)-triene-17-one with 2,2-dimethyl-propane-1,3-diol.[4] Next, C6 was oxidized, affording compound **1** ($KMnO_4$, Adogen 474, aq. $NaHCO_3$, benzene)[6]. Reduction of **1** with $NaBH_4$[7] in methanol afforded 6α-OH-**2**, where the benzoate group was cleaved. Reaction of compound **2** with *p*-TsOH in benzene at reflux temperature[7] and further reaction in acetone to affect a total cleavage of the 17-acetal afforded compound **3**, albeit only in 20 % yield as the only compound obtained (Scheme 1).



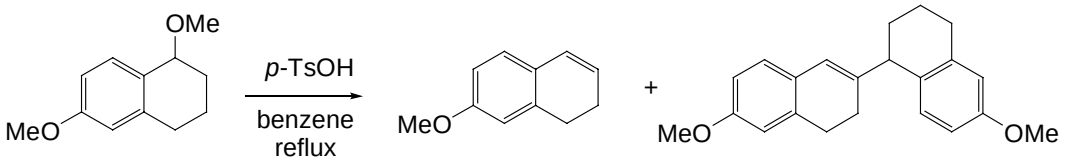
1 **2** **3** Y = 20 %

i) $NaBH_4$, methanol, rt; ii) *p*-TsOH, benzene, reflux temperature; iii) acetone, rt

Scheme 1: Preparation of the estra-1,3,5(10),5-tetraene-3-ol-17-one under acid catalysis

Other conditions were tried. Reaction with Amberlyst 15[8] gave a similar result to that with *p*-TsOH. As Amberlyst 15 is an acidic ion-exchange resin, potential dehydration again would proceed via benzylic carbocation formation, indicating that in general the

carbocation formed undergoes side reactions, probably by intermolecular reaction with the electron rich A-ring to form oligomeric and polymeric products. It must be noted, however, that in the related dimethoxytetrahydronaphthalenes, such as in **4**, dimerisation also occurs between the carbocation of one molecule and the formed product of another.[9]

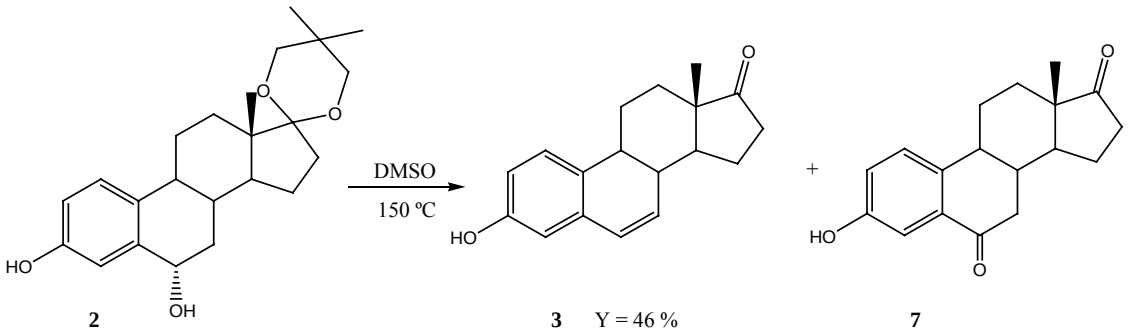


4 **5** **6**

Scheme 2

An alternative to the acid catalysed dehydration is performing the dehydration under basic conditions via tosylates, but previous work by E. Inohae[10] had shown this to be an ineffective way to obtain the olefin, when molecules bear a substitution at positions 7α, due to the adverse stereochemistry of ring B for such an elimination. An approach via transformation of the ketone to the tosylhydrazone with subsequent Shapiro reaction is successful, but involves a tedious route.[7]

In 1962, V. J. Traynelis et al.[11] reported on the thermal dehydration of alcohols in DMSO. This reaction has also once been used in the dehydration of a steroid,[12] but in general it is very infrequently used. In our hands, the reaction of compound **2** in DMSO at 150 ºC after 3 hours afforded compound **3** in 46 % yield. In this reaction another compound was observed, resulting from oxidation of the hydroxyl group at C6 to the carbonyl group (Scheme 3)



2 **3** Y = 46 % **7**

Scheme 3: Preparation of estra-1,3,5(10),6-tetraene-3-ol-one by thermal dehydration

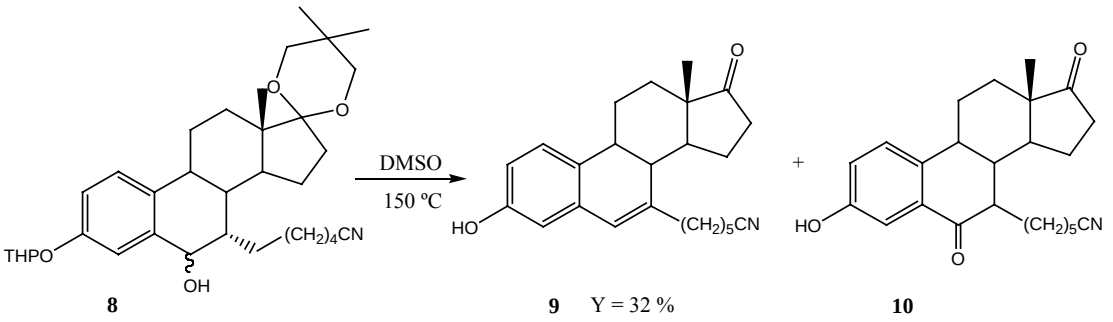
When the reaction was carried out in diphenyl ether at 160ºC, the hydroxyl underwent preferentially oxidation to the carbonyl group. This oxidation in diphenyl ether at high temperatures has been witnessed for other benzylic alcohols in our group, although also in these cases the corresponding olefin forms as a by-product.

Next, the reaction was tried with the more sensitive 7-cyanoalkyl-6-hydroxyestrone **8**. For the preparation of **8**, a strong base was used to introduce the alkyl group at 7 via the enolate of the protected 6-ketoestrone. First, the previously introduced 3-benzoyl protective group had to be replaced by a protective group stable in basic conditions. THP was chosen as the new protective group and 7α-(5'-cyanopentyl)-3-tetrahydropyranoyl-6-oxo-estra-1,3,5(10)-triene-17,17-dimethyldioxane was prepared in the usual way (DHP, *p*-TsOH, CH_2Cl_2). Reduction of this compound gave 6-hydroxy substituted **8** as a mixture of diastereomer 6α/6β-OH.

It is well known that the tetrahydropyranyloxy group is easily removed under mild acidic conditions, being immediately removed under the conditions used in the dehydration. The acetal group undergoes only partial deprotection. When compound **8** was submitted to dehydration with *p*-toluenesulfonic acid in refluxing benzene, even after 15 min, a dark brown solution was observed. After chromatography on silica gel of the reaction mixture, the main compound obtained showed a molecular mass twice that of the desired product [MS (FAB^+, 3-nitrobenzyl alcohol) *m/z* (%) 726 (M^+, 0.18), 727 (MH^+, 0.61); HRMS Found 726.4389, calcd for $C_{48}H_{58}O_4N_2$ (M^+) 726.4397]. No dehydrated monomeric compound was obtained under these conditions. When compound **8** was thermally reacted in DMSO, however, where an oil bath pre-heated at 150 ºC was used, TLC analysis showed 2 compounds after 3h, both of which were not identical with the dimer isolated above. After the column chromatographic separation on silica gel, two pure compounds were obtained, with the first compound eluted being the desired compound **9**.

The dehydration in DMSO is a very temperature sensitive reaction. Carrying out the reaction at temperatures slightly below 150 ºC, affords compound **10** as well as the 6-hydroxyl derivative **8**, but deprotected at positions 3 and 17. In this case, an insignificant quantity of **9** was also observed. Higher temperatures lead to oxidation of the 6-hydroxy group.

The hydrolysis of the acetal in 17 might be promoted by water in the DMSO, part of which may stem from the dehydration itself. The deacetalisation with such comparatively small amounts of water and in a medium of low acidity is helped by the high reaction temperature.



8 **9** Y = 32 % **10**

Scheme 4: Preparation of 7-(5'-cyanopentyl)-estra-1,3,5(10),6-tetraene-3-ol-17-one by thermal dehydration

The deprotection of the phenolic group at C3 provides a less hindered aromatic A ring, more susceptible to reactions, incl. the attack of the carbocations (see above). A small contribution may also be of electronic nature due to the different characters of the methoxy and hydroxy (phenolic) functionalities. This overall difference plays a large role in the dehydration of benzylic alcohols, when carbocationic intermediates play a dominant role. In the case of the thermal dehydration in DMSO, the original paper by Traynelis et al reports that the structural requirements for a successful dehydration are for the alcohol to be either benzylic (secondary or tertiary) or tertiary aliphatic. Traynelis et al. exclude a simple thermal elimination of water as pure alcohols, when subjected to the reaction conditions, produced little or no olefins. They proposed the

formation of a cyclic six-membered transition state as formulated in Fig. 2. An E2 elimination pathway would require that the sulfoxide oxygen serves as a base to abstract the *β*-hydrogen with subsequent elimination of a hydroxide ion, with the cyclic six membered transition state arising from a molecular association between the alcohol oxygen and the sulfur of dimethyl sulfoxide (utilizing the vacant *d* orbitals of sulphur) resulted. [11] Although steroids **2** and especially **8** allow for little conformational flexibility needed to achieve the transition state presented in Fig. 2, it can be ascertained that there is a qualitative difference between the thermal reaction with DMSO and a dehydration involving benzylic cations as intermediates.

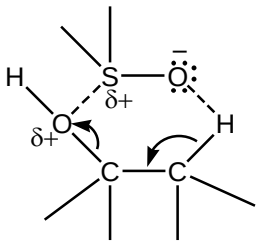


Figure 2

Conclusion

The common acid catalysis to promote the dehydration of benzylic alcohols has been shown to be ineffective in cases where a free phenolic function is located in the *meta* position. Here, oligomerisation and polymerization products dominate.

The problem can be overcome partially by performing the reaction in DMSO, promoting a thermal dehydration. Although the exact mechanism involved is not well understood, it is likely that a benzylic cationic intermediate is not involved.

The advantage of applying the described process in the preparation of C7-substituted estratetraenes is evident. The molecules obtained will undergo further transformations at positions 17 to form substituted estradiol derivatives, which will be radioiodinated.

Experimental

Melting points were measured on a Yanaco microscopic hotstage and are uncorrected. Infrared spectra were measured with JASCO IR-700. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL EX-700 spectrometer (^{1}H at 270 MHz, ^{13}C at 67.8 MHz). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer. Column chromatography was carried out on Wakogel 300.

Estrone (WAKO) and Amberlyst 15 were acquired commercially. Dimethyl sulfoxide was used without further treatment.

Estra-1,3,5(10),6-tetraene-3-ol-17-one (3) A solution of 6α-hydroxy-estra-1,3,5(10)-triene-17,17-dimethyldioxane (51 mg, 0.13 mmol) in DMSO (1.5 mL) was heated at 150 ºC for 3 h. Thereafter, ether (30 mL) was added, and the mixture was extracted with

water (30 mL) The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The crude product was submitted to column chromatographic separation on silica gel (ether/ *n*-hexane/ chloroform 1:1:1) affording **3** (17 mg, 46 %) as a colourless solid. Mp: 264-269ºC (Lit.[13] mp 261-263 ºC); IR (KBr) ν 3428, 2936, 2856, 1719, 1615, 1572, 1494, 1468, 1289 cm^{-1}, ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (s, 3H), 1.25-2.56 (m, 11H), 4.63 (s, 1H, OH), 6.07 (d, 1H, ^3J 9.5 Hz), 6.48 (dd, 1H, ^4J 2.7 Hz ^3J 9.5 Hz), 6.60 (d, 1H, ^3J 2.97 Hz), 6.67 (dd, 1H, ^4J 2.97 Hz ^3J 8.1 Hz), 7.11 (d, 1H, ^3J 8.1 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 13.63, 21.53, 23.75, 31.10, 35.76, 38.23, 42.08, 48.50, 48.77, 113.15, 113.46, 124.52, 128.33, 131.05, 131.24, 135.53, 154.10, 220.43; MS (EI^+, 70 eV) *m/z* (%) 157 (46), 268 (100); HRMS (EI^+) Found: 268.1463, calcd for $C_{18}H_{20}O_2$ 268.1463.

7-(5'-Cyanopentyl)-estra-1,3,5(10),6-tetraene-3-ol-17-one (9) A solution of **8** (85 mg, 0.15 mmol) in DMSO (2 ml) was stirred at 150 ºC for 2h 30 min. Thereafter, the reaction mixture was cooled down, ether was added (30 ml), and the mixture was extracted with water (30 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude material was submitted to column chromatography on silica gel (*n*-hexane/ethyl acetate 1:1) to providing **9** (18 mg, 32%) R_f (*n*-hexane/ethyl acetate 1:1) 0.48; mp 170.5-173 ºC (ether/*n*-hexane); IR (KBr) ν

3424, 2936, 2248, 1732, 1603, 1440, 1249, 1230, 892 cm-1; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.92 (s, 3H), 1.27-2.56 (m, 21H), 6.20 (s, 1H), 6.54 (d, 1H, ^{4}J 2.7 Hz), 6.64 (dd, 1H, ^{4}J 2.7 Hz ^{3}J 8.3 Hz), 7.12 (d, 1H, ^{3}J 8.3 Hz); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ 14.04, 17.15, 24.10, 25.32, 25.54, 27.85, 28.57, 30.74, 35.45, 35.81, 41.65, 41.80, 47.41, 49.64, 112.04, 112.89, 119.58, 124.62 (this peak is larger, it might be 2 C), 130.54, 135.58, 145.37, 154.60, 220.29; MS (FAB^+, 3-nitrobenzyl alcohol) *m/z* 363 (M^+, 2.6), 364 (MH^+, 1.35); HRMS Found 363.2198, calcd for $C_{24}H_{29}O_2N$ (M^+) 363.2198; and 7-(5'-cyanopentanyl)-6-oxoestra-1,3,5(10)-triene-3-ol-17-one (**10**) (29 mg, 46 %) R_f (n-hexane/ethyl acetate 1:1) 0.32; IR (KBr) ν 3444, 2926, 2850, 2240, 1730, 1654, 1608, 1493, 1283, 1259, 1130, 905, 830, 736, 560 cm-1; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.91 (s, 3H), 1.27-2.56 (m, 21H), 2.75 (1H), 5.70 (s, 1H, OH), 7.08 (dd, 1H, ^{4}J 2.7 Hz ^{3}J 8.6 Hz), 7.30 (d, 1H, ^{3}J 8.6 Hz), 7.54 (d, 1H, ^{4}J 2.7 Hz); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ 13.61, 17.04, 20.89, 23.61, 25.25, 26.27, 26.44, 28.61, 31.44, 35.54, 37.40, 42.01, 45.88, 47.79, 48.01, 113.50, 119.58, 121.64, 127.52, 132.03, 137.99, 154.79, 219.54, 200.53; MS (FAB^+, 3-nitrobenzyl alcohol) *m/z* 380 (MH^+, 5); HRMS Found 380.2223, calcd for $C_{24}H_{30}O_3N$ (MH^+) 380.2226.

Acknowledgments

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