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SYNTHESIS OF "3+1" MIXED-LIGAND OXORHENIUM(V) COMPLEXES CONTAINING MODIFIED 3,17β-ESTRADIOL

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Abstract: Two rhenium "3+1" mixed-ligand complexes bearing an estradiol moiety were prepared. The small-sized rhenium chelate units were introduced by two different rhenium precursors to give stable complexes in satisfactory yields.

The introduction of technetium into steroid hormones, either by coupling to the complete molecule or by constructing steroid mimic moieties, opens a promising path to receptor binding technetium-99m radiotracers which are able to image hormone depending tumours[1,2]. In order to investigate the possibilities of labelling steroids with the readily available radionuclide technetium-99m, a number of attempts have been made to label steroids with metal cores by using various N- and S-coordinated chelate systems[3,4,5] or by organometallic complexes[6,7]. The compounds obtained so far with the chelate method are unstable in biological media and because of their bulk and hydrophobicity the affinities for the receptor are in general low. Also, complexation often leads to stereoisomeric complexes. On the other hand a new synthetic strategy by S. Top et al.[7] using organometallic fragments results in rhenium complexes of 3,17β-estradiol with a high affinity for the estrogen receptor. Such compounds as 11β-chloromethyl-17α-[cyclopentadienyl-(rheniumtricarbonyl)-ethynyl]-3,17β-estradiol **A** offer new conjugate approaches in the synthesis of stable and receptor-binding complexes.

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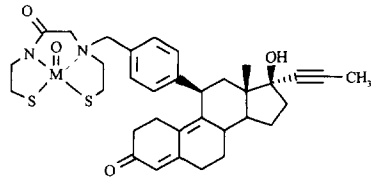
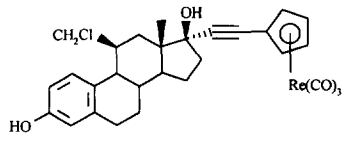


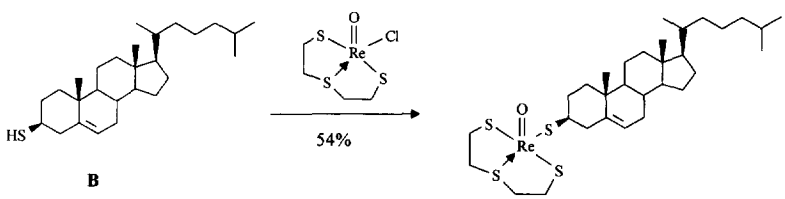
Typical N_2S_2 chelate complex[3,4,5]

M = ^{99}Tc, ^{99m}Tc, Re



Organometallic complex **A**[6,7]

By way of extending our current research aimed at technetium tracers that are active *in vivo*, efforts are being made to explore small-sized neutral mixed-ligand complexes[8] for the design of steroid complexes of both technetium and rhenium. The latter element is involved in our investigations as an inactive model for the radioactive technetium. The principle of preparing neutral mixed-ligand complexes in which small-sized chelate units are bound to steroids was first applied to thiocholesterol **B** as a monodentate ligand in an earlier work (Scheme 1)[9].



B

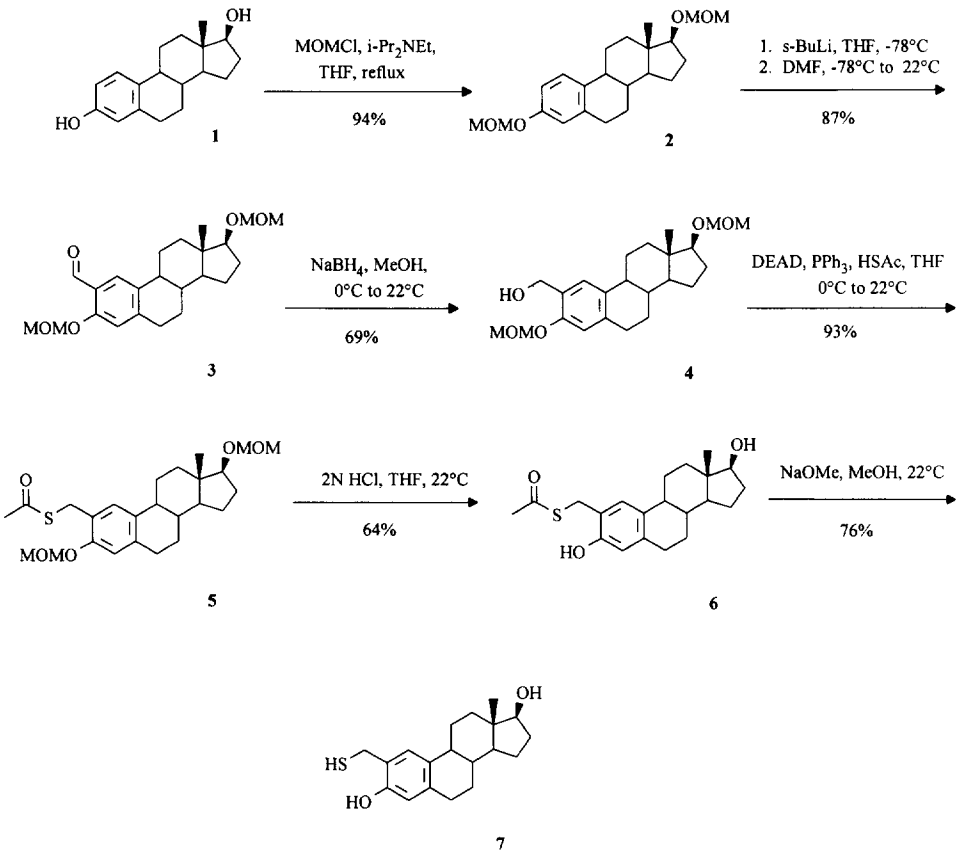
Scheme 1

The binding of metals to a monodentate steroid moiety according to the mixed-ligand concept requires the presence of a suitable donor group. For technetium and rhenium at oxidation state (V), a mercaptide sulphur is the preferred group to provide stable binding of the metal. Therefore chemical modifications of the steroid skeleton should aim at installing a thiol group in the steroid molecule which is capable of forming "3+1" mixed-ligand complexes.

The present article describes some first investigations of the chemistry of estradiol-rhenium complexes starting from easily available 2-substituted estradiol derivatives[10] acting as monodentate ligands. The two representative complexes **10** and **12** are meant to illustrate the potential of the "3+1" concept[8] to produce neutral, small-sized technetium or rhenium chelates without the formation of stereoisomers.

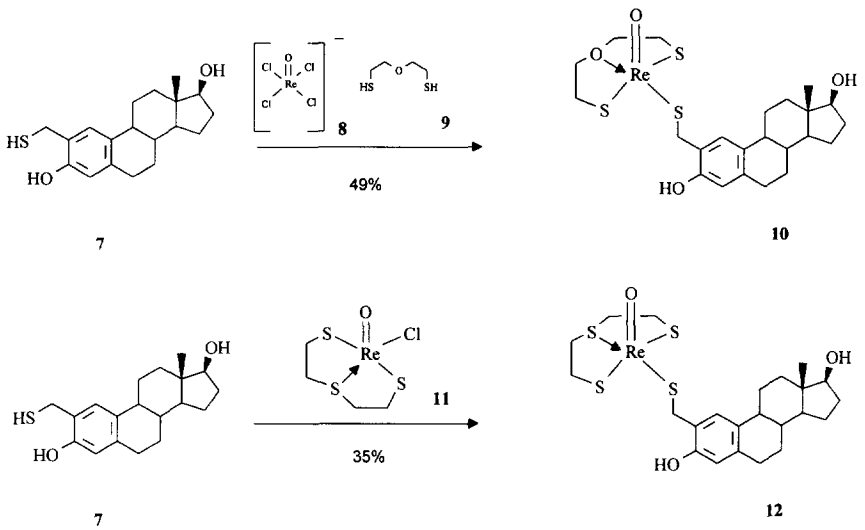
Thiol modification of 3,17β-estradiol was possible by forming a thiolacetate, using the Mitsunobu reaction[11] starting from the corresponding alcohol.

The synthesis of monothiol **7** is shown in Scheme 2. The synthesis started by protecting 3,17β-estradiol **1** with MOMCl to give MOM ether **2**. Deprotonation of **2** with s-BuLi and quenching the intermediate carbanion with DMF only gave the 2-formyl product **3** in a 87% yield. Reduction of **3** with $NaBH_4$ in MeOH led to the alcohol **4**, which was converted with thioacetic acid under Mitsunobu conditions to give the thioester **5**. Cleavage of the MOM-protecting groups with dilute HCl and subsequent saponification of thioester **6** by sodium methoxide gave the desired thiol **7** in a total yield of 25% related to 3,17β-estradiol **1**.



Scheme 2

The complex formation occurs according to the "3+1" concept[8] with two different rhenium precursors **8**[12] and **11**[13] in a 49% and 35% yield respectively (Scheme 3)[14,15]. The complexes differ with respect to the neutral donor atom in the tridentate ligand part, which is O for **10** and S for **12**.



Scheme 3

The common reaction of both the tridentate ligand **9** and the monothiol **7** with the oxorhenium(V) precursor **8** leads to the expected complex **10**. For the preparation of rhenium complex **12** an alternative route is used, based on the chlorine-containing complex **11** as a precursor. Complex **11**[13] is relatively stable but the chlorine can be exchanged by the mercaptide sulphur from steroid thiol **7**. The resulting complexes **10** and **12** are light brown solids which are stable on air and soluble in DMSO with a reddish-brown colour.

The experiments demonstrate the mixed-ligand concept as a useful tool in saturating three of the four coordination sites of the oxometal(V) core with a small tridentate ligand and filling the fourth position with an appropriate coligand. Binding of small-sized metal chelates to biomolecules like steroids with a single donor atom avoids the creation of a new stereogenic centre and may be a suitable procedure for synthesis of metal-containing radiotracers according to a conjugate approach. In further investigations we want to study the influence of the chelate moiety at position 2 and positions such as 17α, 7α or 11β on the receptor-binding properties.

Acknowledgement

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14. 103 mg (175 μmol) of tetra-n-butylammonium-tetrachlorooxorhenate(V) **8** were dissolved in 2 ml of EtOH and cooled to 0°C. At this temperature 61 mg (191 μmol) of thiol **7** and 21 μl (175 μmol) of 3-oxapentane-1,5-dithiol **9** in 2 ml chloroform were added while stirring. Stirring the mixture at 0°C was continued for two hours. During this time a light brown solid was formed. The solid was separated and washed with chloroform. After drying 56 mg (49%) of complex **10** were obtained.
    MS (FAB positive): 677(69.5), 678(14.3), 679(100) M+1+Na^+, 680(20), 681(15,3)
    IR (KBr): (Re=O): 952 cm^{-1}
    Melting point: 170-171°C (decomposition)

15. 36,5 mg (94 μmol) of chloro(3-thiapentane-1,5-dithiolato)oxorhenium(V) **11** were dissolved in 4 ml of hot acetonitrile while stirring. At 80°C 61 mg (192 μmol) of thiol **7**, dissolved in 4 ml of acetonitrile were slowly added, followed by addition of one drop of triethylamine. The colour of the mixture changed immediatly from dark blue to red. The red mixture was stirred at 80°C for 30 min. Then it was evaporated to dryness. The residue was purified by being passed through a silica gel column with $CHCl_3$:MeOH (5:1) as an eluent. After evaporation of the eluate 28 mg (35%) of complex **12** were obtained.
MS (FAB positive): 693(68.1), 694(16.2), 695(100) M+1+Na^+, 696(21.9), 697(20.9) 698(4.8)
IR (KBr): (Re=O): 960 cm^{-1}
Melting point: 186-188°C (decomposition)

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