# Synthesis and Molecular Structure of a Rhenium Complex Derived from 8α-Amino-6-methyl-ergoline☆

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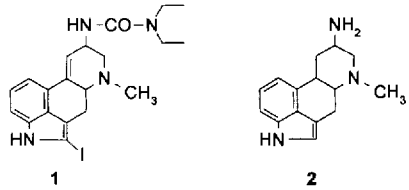
Current research in radiopharmaceutical chemistry is aimed at the design of technetium-based receptor-binding radiotracers because of the excellent nuclide properties of the isotope $^{99m}$Tc. Tc tracers and the corresponding complexes of rhenium, as the inactive surrogate of Tc, are required to imitate organic agonists or antagonists of the receptor. We have started studies with ergolines, which are known to be dopamine substitutes. The present report deals with the functionalization of 8α-amino-6-methyl-ergoline (**2**) with a 2-mercaptoacetyl group, and the subsequent synthesis of the first rhenium complex containing a pendent ergoline moiety [Re-O(SSS)(RS)] (HSSSH = HS–$CH_2CH_2$–S–$CH_2CH_2$–SH and RSH = 8α-amino-*N*-(2-mercaptoacetyl)-6-methyl-ergoline) (**4**). The molecular structure of the rhenium complex was determined by X-ray crystal structure analysis.

Coordination compounds of technetium and rhenium are of great interest for nuclear medical diagnosis ($^{99m}$Tc) and therapy ($^{186}$Re)[1]. Recent efforts have been directed towards the search for $^{99m}$Tc complexes with a high affinity to brain receptors[2]. To access such species, organic receptor-binding ligands are used as lead structures in such a way that an appropriate technetium or rhenium chelate is coupled to them or that non-essential parts of the lead are substituted. Both strategies have been successfully applied recently[2].

In this connection we are interested in the glass of ergot alkaloids[3], derivatives of lysergic acid or ergoline structures, which exhibit a broad range of pharmacological activities and have already been successfully exploited for the development of 2-[$^{123}$I]iodolisuride (**1**) as a SPECT imaging agent in the study of healthy subjects and patients[4].

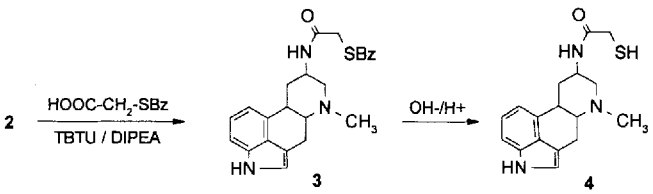
Starting from 8α-amino-6-methyl-ergoline (**2**)[5] we investigated the suitability of the ergolines for the design of dopamine $D_2$ receptor-binding technetium tracers. The congener rhenium was used as a surrogate for the radioactive technetium. For the coupling of the metal to the ergoline moiety we used the "3 + 1" mixed-ligand concept[6]. To enable the ergoline functionality to act as a monodentate ligand in the intended mixed-ligand "3 + 1" complex, a mercapto group had to be introduced. This was achieved according to Scheme 1; thus the *S*-benzoylated ligand **3** was obtained by condensation of the amino group in the parent

Figure 1. 2-[$^{123}$I]Iodolisuride (**1**) and 8α-amino-6-methyl-ergoline (**2**)




8α-amino-6-methyl-ergoline (**2**) with benzoylmercaptoacetic acid by means of *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium-tetrafluoroborate (TBTU)[7] and diisopropyl ethyl amine (DIPEA) in *N*-methylpyrrolidone. Immediately before complexation, the benzoyl group was removed by sodium methylate to give, after neutralization with diluted hydrochloric acid, the free mercaptane 8α-amino-*N*-(2-mercaptoacetyl)-6-methyl-ergoline (**4**).

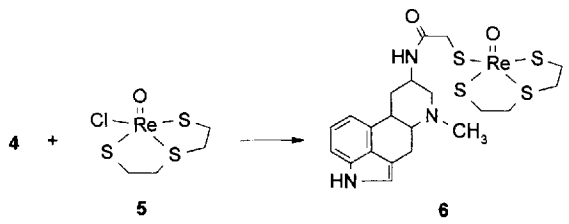
Scheme 1. Synthesis of ligand **4**




  0009–2940/97/0707–0839 $ 17.50+.50/0 

For preparation of the rhenium complex **6**, the mercaptane **4** was allowed to react with [ReO(SSS)Cl] (**5**)[8] as a performed metal/tridentate unit. The chlorine ligand was substituted by **4** (Scheme 2) to yield brown crystals of **6** in moderate yield (not optimized). This compound is stable in solid form and in solution and there is no indication of cleavage of the monodentate ligand.

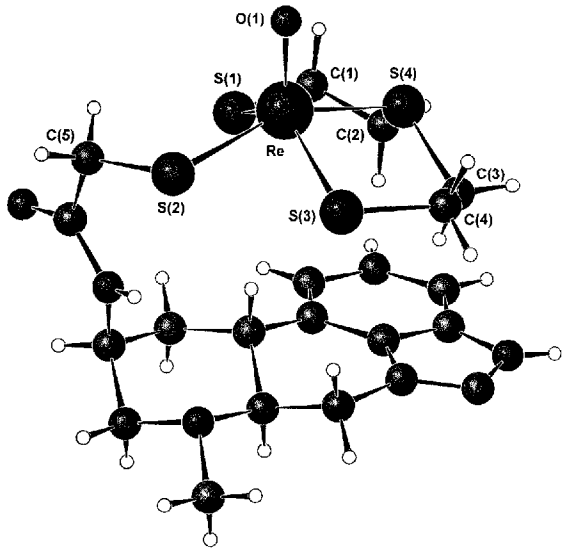
Scheme 2. Synthesis of the rhenium complex **6**




**5** **6**

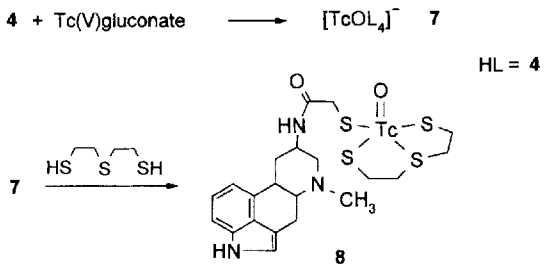
The X-ray crystal structure determination of compound **6** (Figure 2) reveals the formation of a five-coordinated complex. The tridentate ligand and the mercaptide of **4** possess equatorial positions in the square-pyramidal geometry as is typical of sulphur-coordinated "3 + 1" oxorhenium(V) complexes[8,9].

Figure 2. Molecular structure of complex **6** (powder cell); selected bond distances [Å] and angles [°]: Re–O(1) = 1.659(7), Re–S(1) = 2.282(2), Re–S(2) = 2.315(3), Re–S(3) = 2.299(2), Re–S(4) = 2.364(3), S(2)–C(5) = 1.815(10); O(1)–Re–S(1) = 114.5(3), O(1)–Re–S(2) = 105.5(3), O(1)–Re–S(3) = 115.6(3), O(1)–Re–S(4) = 99.7(3), S(1)–Re–S(2) = 89.61(8), S(3)–Re–S(2) = 80.82(11), C(5)–S(2)–Re = 114.5(3).




The idea of coupling the mercapto-functionalized ergoline to the metal is applicable, in a modified form, to the preparation of radioactive technetium complexes. Reaction of **4** with Tc(V) gluconate results in the formation of an intermediate, which is most probably $[TcO(L)_4]^-$ (**7**). Partial substitution of **4** by the tridentate ligand leads to the mixed-ligand Tc complex **8** according to Scheme 3. A solution of the radiochemically pure Tc complex **8** was obtained by HPLC: the $R_t$ value ($R_t$ = 19.1 min) was analogous to that of the rhenium complex **6**.

Scheme 3. Formation of the technetium complex **8**




**8**

The transformation of a technetium or rhenium chelate into a mimic of a receptor-binding lead is an important issue in Tc tracer design. As for the chelate, the relatively small "3 + 1" chelate is an advantageous alternative to other chelate systems when used, for example, to bind technetium to steroids[10]. The preparation and characterization of the first rhenium complex containing an ergoline moiety as described here has paved the way to synthesis of the corresponding Tc species and investigations into the relationship between the structure and receptor-binding ability of radioactive coordination compounds.

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## Experimental Section

*Compound* **3**: A mixture of 98 mg (0.5 mmol) *S*-benzoylmercapto acetic acid, 165 mg (0.5 mmol) TBTU and 170 µl (1 mmol) DIPEA in 1 ml *N*-methylpyrrolidone was stirred for 3 min and added dropwise into a solution of 96 mg (0.4 mmol) 8α-amino-6-methyl-ergoline (**2**) in 1 ml *N*-methylpyrrolidone. After stirring for 4 h, the reaction product was purified by MPLC (RP8, eluent 0.1% TFA/acetonitrile). Evaporation of the solvent yielded **3** as a light brown solid (yield 20%); m.p. 175°C. – $C_{17}H_{21}N_3OS$ (315.43): calcd. C 64.73, H 6.71, N 13.32, S 10.16; found C 64.51, H 6.42, N 13.18, S 10.25.

*Compound* **4**: Saponification of **3** in sodium methylate/methanol, neutralization with hydrochloric acid, and purification by MPLC as described for **3** gave **4** in a yield of ca. 30%; m.p. 152°C. – $^1$H NMR (400 MHz, δ[D$_6$]DMSO = 2.51): δ = 1.87 (t, 1H, $J$ = 12.5 Hz, $CH_2$), 2.69 (d, 1H, $J$ = 13.5 Hz, $CH_2$), 2.79 (t, 1H, $J$ = 7.7 Hz, SH), 2.88–2.94 (m, 1H, $CH_2$), 2.98 (s, 3H, N–$CH_3$), 3.16–3.30 (m, 2H, CO–$CH_2$–S), 3.39–3.59 (m, 6H, + $H_2O$, CH- and $CH_2$), 3.73 (t, 1H, $J$ = 11.6 Hz, CH- or $CH_2$), 4.24 (s, 1H, >CH–N), 6.88 (d, 1H, $J$ = 6.8 Hz, arom.), 7.08–7.12 (m, 2H, arom. and olefin.), 7.23 (d, 1H, $J$ = 8.2 Hz arom.), 8.39 (s, 1H, NH–chain), 10.91 (s, 1H, NH–ring).

*Rhenium Complex* **6**: To a solution of 42 mg (0.1 mmol) **3** in 1 ml DMSO, a solution of sodium methylate (1.25 M, 0.15 ml) was added under a nitrogen atmosphere. After stirring for 1 h the mixture was neutralized with methanolic hydrochloric acid. A solution of 39 mg (0.1 mmol) **5** in 5 ml acetonitrile was added dropwise to this mixture. After stirring the mixture for 2 h then allowing it to stand overnight, the sodium chloride was filtered off and the solvent was reduced to a small volume. DMSO was added and the mixture was purified by column chromatography [silica gel 60 (Merck), methanol/conc. ammonia solution (95:5)]. After reducing

the volume of the methanolic solution, dark red crystals were obtained (yield ca. 20%); m.p. 247–250°C. – IR (KBr): $\tilde{\nu}$ = 968 $cm^{-1}$ (Re=O). – $C_{21}H_{28}N_3O_2S_4Re$ (669.06): calcd. C 37.71, H 4.22, N 6.28, S 19.17; found C 37.60, H 3.99, N 6.40, S 18.96.

*HPLC Characteristics of the Technetium Complex* **8**: Column: 250 × 4 mm, RP18 (Eurosphere), flow rate: 1 ml/min, eluent A: 0.01 M phosphate buffer, pH = 5.8, eluent B: acetonitrile, elution: 5 min 75% A, 25% B; 15 min from 75% A, 25% B to 10% A, 90% B; 5 min 10% A, 90% B, detection: UV and radioactivity, $R_t$ = 19.1 min.

*X-ray Crystal Structure Analysis of* **6**: Single crystals were obtained by slow evaporation of a methanolic solution of **6**. $C_{21}H_{28}N_3O_2S_4Re$ (668.90). Monoclinic space group *P*2 (1) (Nr. 4), $a$ = 9.265(1) Å, $b$ = 11.784(4) Å, $c$ = 11.233(2) Å, β = 94.25(1)°, $V$ = 1223.1(5) $Å^3$, $Z$ = 2, $D_c$ = 1.813 $Mg/m^3$, μ = 5.332 $mm^{-1}$, (Mo-$K_\alpha$), $F$(000) = 658. A dark red crystal of dimensions 0.72 × 0.54 × 0.27 mm was mounted to an Enraf-Nonius CAD4 diffractometer (graphite monochromator scaled Mo X-ray tube λ = 0.71069). Intensity data were collected by the Θ-2Θ scan technique in the range 2Θ 1.82–50° with index ranges $0 < h < 11$, $0 < k < 13$, $-13 < l < 13$. A total of 2408 independent reflections were measured, of which 2262 with $I$ ($hkl$) > 2σ ($I$) were considered to be observed and were used for structure determination. The data were corrected for Lorentz, polarization, and X-ray absorption effects. Systematic monitoring of two check reflections at regular intervals showed a loss in intensities of 3.3%. Positions of Re and S atoms were determined by direct methods using MULTAN[11]. By several cycles of difference Fourier synthesis and full-matrix least-squares calculations all other atoms were located. The positions of the hydrogen atoms were calculated and refined as riding. The final refinement (on $F_O^2$ data) of atomic coordinates and anisotropical thermal parameters was carried out with SHELXL-93[12]. Values for the atomic scattering factors $f'$ und $f''$ were taken from ref.[13]. This refinement converged at $R_1(F_O^2)$ = 0.0253 and conventional $R_2(F_0)$ = 0.0668. Complete details of the data collection and refinement process can be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany, on quoting the depository number CSD 405989.

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☆ Dedicated to Professor *Roland Mayer* on the occasion of his 70th birthday.


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