Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 23, pp. 2871-2874, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00533-1

Retropane - a new Rhenium Complex as a potential Ligand to label the Dopamine Transporter

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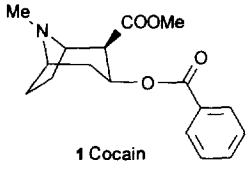
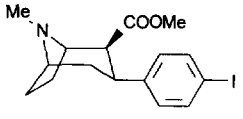
Abstract: The synthesis of a new mixed-ligand rhenium complex containing the α-tropanol moiety is reported. The compound is a predecessor to the analogous technetium-99m complex for SPECT imaging of the dopamine transporter in the brain. Copyright © 1996 Elsevier Science Ltd

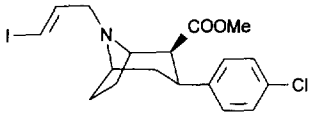
Radiolabelled phenyltropanes as a class of ligands with high affinity to the dopamine transporter offer many possiblities for nuclear medical diagnosis of dopamine receptor depending alterations of the brain. So far, ^{11}C, ^{18}F, and ^{123}I-labelled β-CIT[1,2] [N-methyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane] **1** and IPT[3] [N-(3-idopropen-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl)tropane] **3** have been proposed as PET and SPECT tracers for the diagnosis of Parkinson's disease.



1 Cocain



2 β-CIT



3 IPT

However, short half-life, very high costs and practical and logistical expenditures in the application of cyclotron-nuclides ^{11}C or ^{18}F as well as ^{123}I make desirable to substitute these nuclides by ^{99m}Tc, a generator-nuclide with ready availability.

Recently, first cocaine derivatives containing technetium or its congener rhenium[4,5] have been published. They represent substituted phenyltropanes bearing a chelate moiety at the tropane nitrogen.

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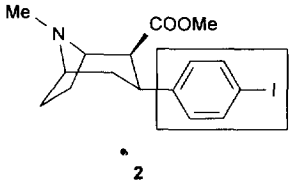
Neumeyer[6] has recently reported on the attachment of a tetradentate N_2S_2 chelating unit to the β-CIT system by substitution of the methoxy group in the ester functionality.

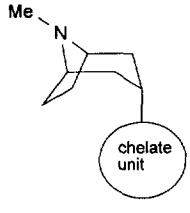
We would like to report on the synthesis of the first rhenium complex „retropane", alternatively derived from the basic skeleton of the tropane molecule modified at the C_3 position. This contribution is part of our work to make available Tc tropane complexes with high affinities to dopamine transporters as potential radiopharmaceuticals.

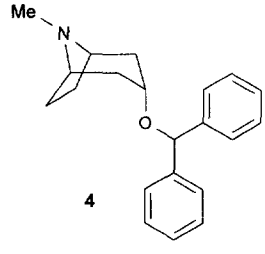
To bind the metal, we make use of the „3+1"-principle for designing mixed-ligand complexes of Tc and Re. This route consists in binding of the oxometal(V) group at a mercaptide sulfur of the parent molecule and blocking of the remaining free coordination sites by a tridentate S,X,S donor chelating ligand (HSXSH = HS-CH_2CH_2-X-CH_2-CH_2-SH, X = O, S, NR)[7]. This method offers the possibility of preparing small-sized chelate units attached to the biological relevant substituent. An additional advantage is that only one donor atom has to be introduced in the biomolecule.

Since benztropane analoges such as **4**[8] as well as a couple of other metal complexes containing the tropane system, such as η^6-(2β-carbomethoxy-3β-phenyl-tropane) chromium and ruthenium, exhibit a great affinity to the dopamine transporter[9] we decided to renounce the carbomethoxy group in the 2-position of β-CITand to substitute the iodophenyl moiety by a monodentate mercapto functionality which becomes part of the chelate upon reaction with [ReO(SSS)Cl].



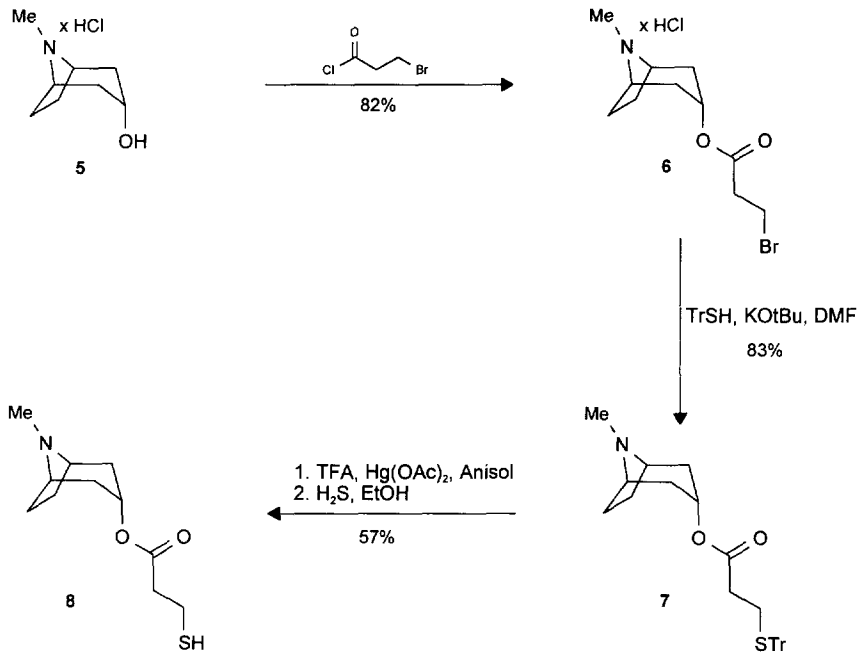
2





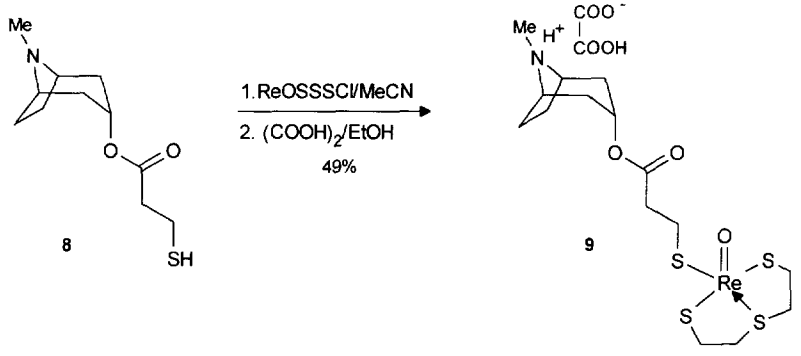
4

The introduction of a mercapto group was achieved in form of ω-mercapto-substituted esters of tropanol. Starting from α-tropanol hydrochloride (**5**) the 3-bromopropionic acid tropylester (**6**) was synthesized by a very simple procedure[10]. The resulting hydrochloric salt is reacted with triphenylmethanethiol in DMF to yield the S-protected mercaptan (**7**) in 83 % yield. The deprotection of the mercapto group is accomplished by reacting the thiotritylated compound with mercury acetate in trifluoro acetic acid and cleaving the mercury-mercaptid with hydrogensulfid.



Scheme 1

The 3-mercapto propionic acid tropylester (**8**) is received in about 40% yield by this procedure. The rhenium complex (**9**) was obtained in a typical 3+1-reaction, in which the thiol as the monodentate ligand was reacted with the $[ReO(SSS)Cl]$[11] in acetonitrile to give the complex in a yield of about 50 %. Purification of the complex was accomplished by chromatography on silica gel. The red oil obtained has been crystallized as oxalate salt.



Scheme 2

To summarise, we were able to synthesize the first rhenium complex based on a O-substituted tropanol derivative. Extension of the work will refer to other esters of tropan, preparation of the congener technetium complexes and testing of affinity to dopamine transporter (DAT).

Acknowledgement. Financial support of this work by the Deutsche Forschungsgemeinschaft is gratefully acknowledged. We thank Mrs. S. Machill and Mrs. A. Rudolph from the Dresden University of Technology for recording the mass and nmr-spectra.

References and Notes

Analytical data for **9:**

^{1}H NMR (500 MHz, CD_3OD): δ 2.13-2.15 (m, 4H), 2.32-2.36 (m, 2H), 2.43-2.47 (m, 2H), 2.52-2.57 (m, 2H), 2.85 (s, 3H, CH_3), 2.98 (t, J= 6.85Hz, 2H, CH_2), 3.13 (td, J_1= 13.65 Hz, J_2= 2.78Hz 2H), 3.93 (bs, 2H), 4.06 (t, J= 6.85Hz, 2H, CH_2), 4.12 (dd, J_1= 10.74 Hz, J_2= 3.37 Hz, 2H), 4.37 (dd, J_1= 13Hz, J_2= 4.77Hz), 5.13 (t, J= 4.6Hz, 1H)
^{13}C NMR (125.77 MHz, CD_3OD): δ 24.89, 32.60, 36.03, 39.07, 39.46, 47.41, 48.49, 63.88, 65.63, 165.46, 172.97
MS (FAB positiv): 582(54.3), 583(10.5), 584(100) M^+ +1, 585(19), 586(17), 587(3), 588(1.4)
IR (KBr): ν ReO: 960 cm^{-1}
EA: (oxalate) calculated for $C_{17}H_{28}NO_7S_4Re$ in brackets : found C: 30.41(30.31), H: 4.33(4.19), N:2.20(2.08), S: 17.92(19,00)

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(*Received in Belgium* 6 *August* 1996; *accepted* 31 *October* 1996)