Novel Cyclopentadienyl Ruthenium(II) Complexes of Biologically Important Compounds

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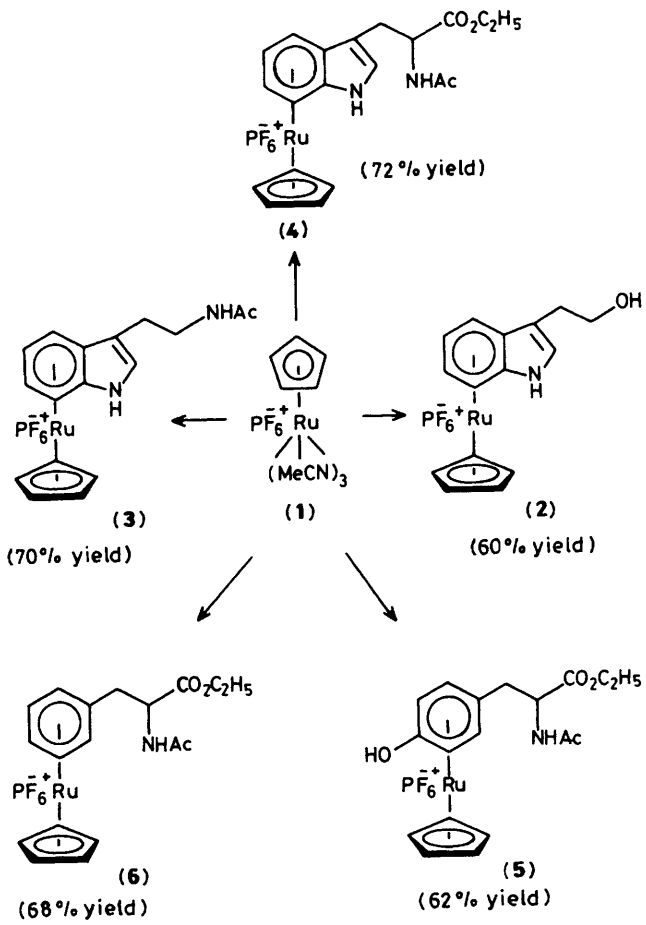
New cyclopentadienyl ruthenium complexes of tryptophol, *N*-acetyltryptamine, *N*-acetyl-L-tryptophan ethyl ester, *N*-acetyl-L-phenylalanine ethyl ester, and *N*-acetyl-L tyrosine ethyl ester were prepared by thermal ligand exchange reaction between cyclopentadienyl-tris(acetonitrile)ruthenium hexafluorophosphate and the substrate in 60—80% yields.

Ruthenocene and its derivatives are finding increasing biochemical applications in the area of metallopharmaceuticals.[1] For example, radiolabelled ruthenocenylalanine has been evaluated as a pancreatic imaging agent.[2] In connection with a programme directed towards developing new methods for the regiospecific synthesis of substituted indoles, we synthesized (η^6-4- or 5-chloroindole)Ru(η^5-Cp)hexafluorophosphates (Cp = cyclopentadienyl).[3] We now report the attachment of the organometallic moiety ($CpRu^+$) onto the aromatic ring of biologically active compounds, specifically, tryptophol, *N*-acetyltryptamine, and the ethyl esters of *N*-acetyl-L-tryptophan, *N*-acetyl-L-phenylalanine, and *N*-acetyl-L-tyrosine.



Scheme 1

These novel complexes are of potential interest as radiopharmaceuticals (^{97}Ru, ^{103}Ru, ^{106}Ru), in metalloimmunoassay,[4] and in the synthesis of neuropeptides containing terminal tyrosine and alanine (enkephalin,[5] human-β-endorphin,[6] and peptide T[7]).

Thermal exchange between $[CpRu(MeCN)_3]PF_6$ and simple arenes,[8] and cyclophane and polycyclic aromatic hydrocarbons[9] has been reported, but our work using substituted indoles as ligands demonstrated the application of this process to more complex systems.[3] Scheme 1 illustrates the methodology applied to protected amino acids. The cyclopentadienylruthenium complexes (**2**)—(**6**), were prepared as follows: Under a nitrogen atmosphere, the substrate (1.3 mmol) and $[CpRu(MeCN)_3]PF_6$ (**1**) (1.0 mmol) were heated at 40—50 °C in 1,2-dichloroethane (20 ml) for 15 h. The solvent was removed *in vacuo* and the residue was washed with ether; the solid which remained was recrystallised (acetone–ether) to give the yellow complexes (**2**)—(**6**) in 60—80% yields [based on (**1**)]. These novel complexes are thermally stable, crystalline solids and gave satisfactory analytical and spectroscopic results.† The cyclopentadienyl protons are observed at δ 5.0—5.3, with carbon resonances in the range δ 79—81.

This work establishes that stable $CpRu^{(II)}$ complexes of suitably protected aromatic amino acids of potential biological importance can be synthesized as stable compounds.

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† All new ruthenium complexes were characterized, *inter alia*, by ^{1}H and ^{13}C n.m.r. and combustion analysis.

Selected spectroscopic data for (**3**): ^{1}H n.m.r. [400MHz, $(CD_3)_2CO$] δ 10.27 (s, NH), 7.67 (d, *J* 2.4 Hz, 2-H), 7.24 (s, N*H*COMe), 7.08 (d, *J* 6.0 Hz, 7-H), 7.01 (d, *J* 6.0 Hz, 4-H), 5.96 (t, *J* 5.6 Hz, 6-H), 5.92 (t, *J* 5.6 Hz, 5-H), 5.00 (s, Cp), 3.41—3.56 (m, CH_2CH_2NH), 2.93 (t, *J* 7 Hz, $-CH_2CH_2NH$), 1.88 (s, COMe); ^{13}C n.m.r. [400 MHz, $(CD_3)_2CO$] δ 170.36 (*C*OMe), 134.76 (C-2), 111.31 (C-3), 115.16, 96.18, 81.57, 81.37, 77.01, and 72.30 (Ar-ring), 79.04 (Cp), 39.68 and 25.43 (CH_2's), 22.95 ($COCH_3$).

For (**4**): ^{1}H n.m.r. [400 MHz, $(CD_3)_2CO$] δ 10.29 (s, N*H*), 7.75 (s, 2-H), 7.54 (d, *J* 8 Hz, N*H*COMe), 7.10 (d, *J* 6.0 Hz, 7-H), 7.01 (d, *J* 5.6 Hz, 4-H), 6.00 (t, *J* 5.6 Hz, 6-H), 5.95 (t, *J* 5.6 Hz, 5-H), 5.09 (s, Cp), 4.69—4.75 (m, ABX further coupled to NH, $-CH_2CHNH-$), 4.16 (q, *J* 7 Hz, CO_2CH_2Me), 3.31, 3.14 (q, q, $-CH_2CHNH-$, J_{AB} 14.8 Hz), 1.98 (s, $COCH_3$), and 1.22 (t, *J* 7 Hz, $CO_2CH_2CH_3$); ^{13}C n.m.r. [400 MHz, $(CD_3)_2CO$] δ 171.09 (CO_2Et), 170.99 (*C*OMe), 136.08 (C-2), 110.84 (C-3), 112.59, 96.36, 81.56, 81.46, 76.77, and 72.29 (Ar-ring), 79.22 (CP), 62.13 ($CHCO_2Et$), 54.24 (CO_2CH_2Me), 36.76 ($-CH_2CH-$), 22.60 ($COCH_3$), and 14.37 ($CO_2CH_2CH_3$).

For (**6**): ^{1}H n.m.r. [400 MHz, $(CD_3)_2CO$] δ 7.67 (d, *J* 7 Hz, NH), 6.30 (d, 1 H), 6.26 (d, 1H), and 6.18—6.21 (m, 3H), 5.43 (s, Cp), 4.51—4.68 (m, $-CH_2CHNH-$, ABX further coupled with NH), 4.12 (q, *J* 7.0 Hz, CO_2CH_2Me), 3.08, 2.90 (q, q, J_{AB} 14.0 Hz, $-CH_2CHNH-$), 1.91 (t, *J* 7Hz, $CO_2CH_2CH_2Me$) ; ^{13}C n.m.r. [400 MHz, $(CD_3)_2CO$] δ 170.99 (*C*OEt), 170.63 (NH*C*OMe), 102.23, 87.94, 87.91, 86.16, 86.10, and 85.81 (Ar-ring), 81.31 (Cp), 61.98 ($CHCO_2Et$), 53.97 (CO_2CH_2Me), 36.97 ($-CH_2CH$), 22.50 ($-COCH_3$), and 14.18 ($CO_2CH_2CH_3$).