

*Dedicated to the memory of
Professor Maria Brezeanu (1924–2005)*

NEW DIBENZOBICYCLO[2.2.2]OCTANE DERIVATIVES

Michaela Dina STĂNESCU,^{a*} Adina RUS,^b Maria GIURGINCA^c and Cornelia GURAN^b

^aChemical and Biological Sciences Department, “Aurel Vlaicu” University, Bd. Revolutiei 77, 310130, Arad, Roumania

^bInorganic Chemistry Department, University “Politehnica” of Bucharest, Polizu 1, 78126, Bucharest, Roumania

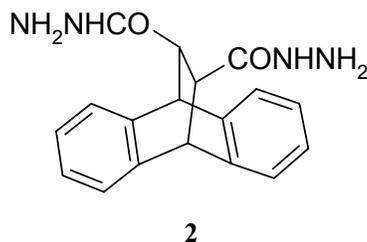
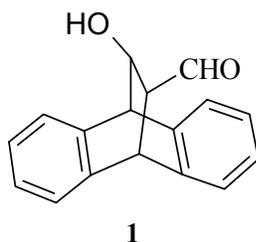
^cPhysical-Chemistry Department, University “Politehnica” of Bucharest, Polizu 1, 78126, Bucharest, Roumania

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The interest for the synthesis and study of the metal complexes of dibenzobicyclic derivatives can be connected with the presence of a potential biological activity in such compounds. Thus, the syntheses of a new ligand belonging to the same family and of a coordination complex with europium(III) of this ligand, are presented. The proposed structures have been confirmed by the IR and NMR spectra. The antioxidative activity of the ligand and the complex are presented.

INTRODUCTION

In previous papers a number of dibenzobicyclo[2.2.2]octane compounds have been studied and it has been shown that they are polydentate ligands.^{1, 2} The coordinative complexes of these compounds have potential biological activity¹⁻³ due to the presence of the polycyclic system and the metal with its redox activity, in the same molecule.



Due to their interesting properties a new compound with the same skeleton has been synthesized and a coordinative compound with europium as metal has been prepared. The selection of Eu³⁺ ion is motivated by the recent applications of lanthanides,⁴ Ln(III) complexes being known as contrast agents for medical resonance imaging (MRI), luminescent stains for fluoroimmunoassays, or catalysts for the selective cleavage of RNA and DNA. The development of tailored receptors for Ln(III) remains an open challenge for synthetic chemists, since Ln(III) ions do not display pronounced stereochemical preferences for particular bonding modes. Also, such compounds may be interesting for displaying antioxidative properties and being used as antioxidants.

RESULTS AND DISCUSSION

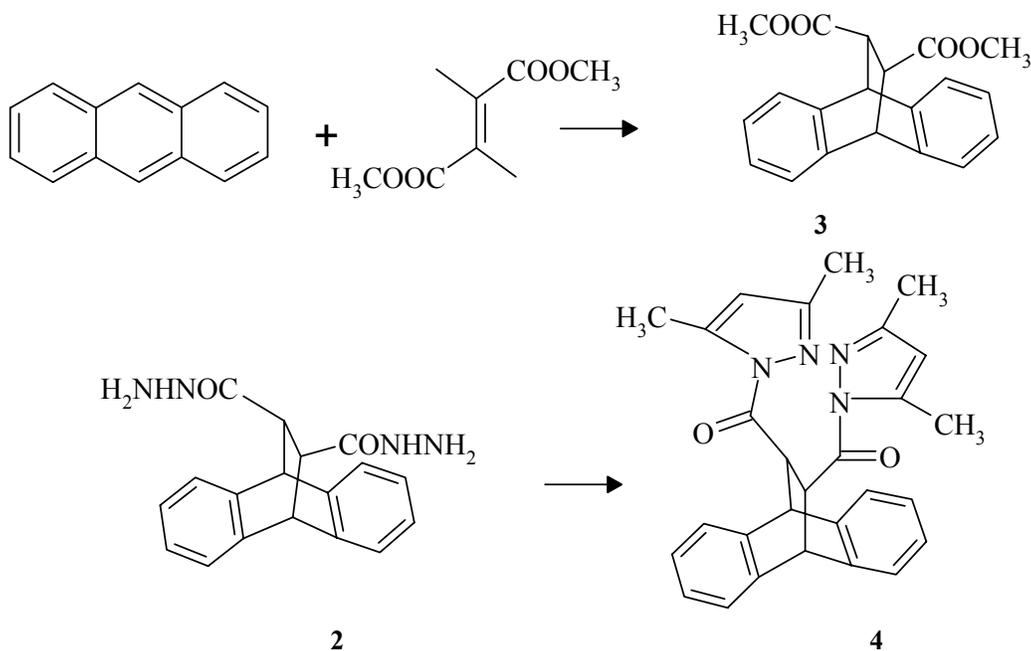
The synthesis of the dibenzobicyclic compounds started with a diene type reaction. Thus, from anthracene and fumaric ester by a diene reaction, presented in Scheme 1, the polycyclic ester **3** has been

*Corresponding author: stanescu@uav.ro

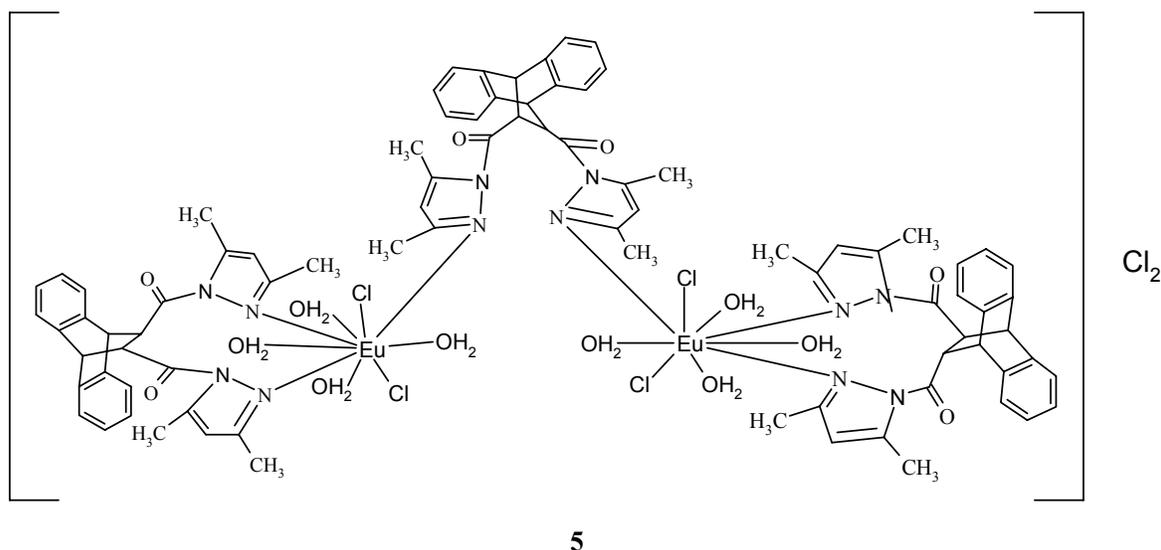
obtained. The reaction takes place only in the presence of AlCl_3 in a molar ratio of 2:1 toward the reagents. According to the literature,⁵ the AlCl_3 leads to the diminishing of the energy of the orbital involved in diene synthesis. The complex formed from fumaric ester and AlCl_3 has the reaction orbital (LUMO) energetically closer to that of anthracene HOMO orbital. As known before,⁶ smaller differences between the diene partner orbital energies lead to a higher reactivity.

The ester has been transformed into the *trans* dihydrazide **2** by a classical nucleophilic substitution of the ester groups on treatment with NH_2NH_2 hydrate as nucleophile.

Starting from compound **2** dipyrazole **4** was synthesized by treatment with diacetyl in acid media. Similar condensation reaction has been previously described.⁷



By the procedure described in the literature,⁸ the polycyclic complex **5** has been obtained, starting from dihydrazide **2** and acetylacetone, in the presence $\text{EuCl}_3 \cdot 6\text{H}_2\text{O}$ and HClO_4 , as catalyst:



The spectral measurements IR (see Experimental) and NMR spectra (Table 1) confirmed the structure of the synthesized compounds.

The study of the $^1\text{H-NMR}$ data showed that the presence of different functional groups influenced especially the positions of the bridge protons. For ester **3** and dihydrazide **2** the bridge protons are more shielded due to the presence in the neighborhood of O and N atoms, rich in electrons. A displacement toward higher values is observed in the pyrazole and the complex, where an attracting electron effect, due to the heteroaromatic moiety of pyrazole, was observed. Moreover, in the complex case, the molecule loses its symmetry so that the aspect of the bridge protons is no more that of a singlet, like in the ligand, each molecule of the ligand involved in the complex having different neighbourhood reflected in the complex aspect of the $^1\text{H-NMR}$, where the bridge protons appeared in the interval 4.57-4.77. The same complex aspect is observed for the bridgehead and the aromatic protons, confirming once more the different electronic environment for the three ligand molecules involved in the complex.

The new synthesized compound, dipyrazole **4**, is, like the starting material dihydrazide **2**, a potential polidentate ligand having numerous donor centers that may be involved in complexation with different transitional metals.³ Compound **4** could also be a possible intermediate for polyamide synthesis.⁹

Table 1

$^1\text{H NMR}$ Spectra of dibenzobicyclo[2.2.2]octane derivatives

Compound	Solvent	Aromatic region	Bridge	Bridgehead	Others
Ester 3	CDCl_3	7.32 m H_1, H_5 ; 7.24 m H_4, H_8 7.11 m H_3, H_7 ; 7.08 m H_2, H_6	3.42 s $\text{H}_{11}, \text{H}_{12}$	4.72 s $\text{H}_9, \text{H}_{10}$	3.62 s CH_3
Hydrazide 2	DMSO	7.29 m H_1, H_5 ; 7.16 m H_4, H_8 ; 7.07m H_3, H_7 ; 7.03 m H_2, H_6	3.10 s $\text{H}_{11}, \text{H}_{12}$	4.50 s $\text{H}_9, \text{H}_{10}$	3.75 NH
Pyrazole 4	CDCl_3	7.38 m H_1, H_5 ; 7.28 m H_4, H_8 ; 7.14m H_3, H_7 ; 7.11m H_2, H_6	4.47 s $\text{H}_{11}, \text{H}_{12}$	4.78 s $\text{H}_9, \text{H}_{10}$	5.86 s CH 2.42 s CH_3 2.00 s CH_3
Complex 5	DMSO	7.45- 7.001 m $\text{H}_1, \text{H}_5, \text{H}_4, \text{H}_8$, $\text{H}_3, \text{H}_7, \text{H}_2, \text{H}_6$	4.37-4.40m $\text{H}_{11}, \text{H}_{12}$	4.57- 4.77 m $\text{H}_9, \text{H}_{10}$	6.99-6.98 m CH 2.35 s CH_3 2.00 s CH_3

In order to see the influence of europium on the behaviour of dipyrazole **4**, its chemiluminescence spectrum was compared with that of complex **5**. As a reference sample, a solution of Luminol and H_2O_2 , at a pH of 8.6, in Tris as solvent, was used. The standard wavelength for the measurements is 430 nm.

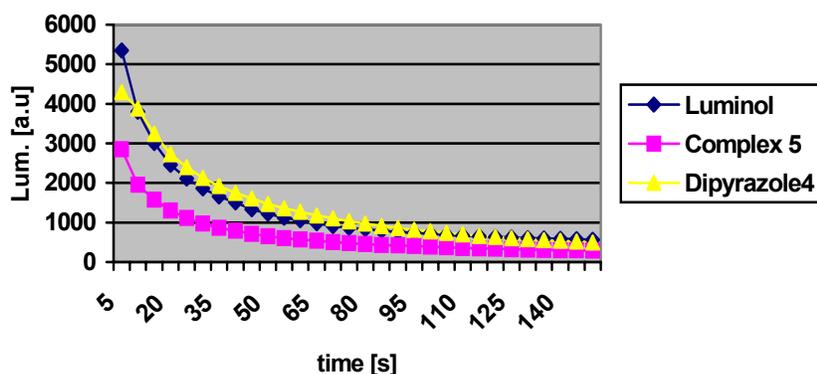


Fig. 1 – The chemiluminescence spectra of dipyrazole **4** and complex **5**.

The absorption spectra are shown in Fig. 1 and reveal that dipyrazole **4** and complex **5** exhibit an antioxidative behaviour. The europium(III) ion increases this property of a ligand alone, from 19.7% to 46.7%. This result gives hopes that complex **5** may be use as contrast agents for medical resonance imagining (MRI), luminescent stains for fluoroimmunoassays, or catalysts for the selective cleavage of RNA and DNA.

CONCLUSION

A new ligand with a complex aromatic structure has been synthesized. The europium complex of this ligand was prepared. Both compounds structure was proposed based on analytical data. The antioxidative activity of the complex was revealed making possible its application in MRI.

EXPERIMENTAL

The synthesis of the compounds **2-5** was performed as described below. The IR spectra of the compounds were recorded with a K. Zeiss Jena UR 20 spectrophotometer and the NMR spectra with a Gemini 300-Varian (with internal TMS) apparatus. The luminescence spectra were carried out on TD 20/20 Turner Designes instrument.

Syntheses of dibenzo[2.2.2]octane derivatives

Dimethyl ester of trans 9.10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid¹⁰ (**3**)

A mixture of anthracene and fumaric dimethylester in the presence of AlCl₃ (molar ratio = 1:1:2) in CH₂Cl₂ was kept at reflux for 2h. The reaction product was decomposing with ice and the organic part separated. The water was extracted twice with CH₂Cl₂ and the reunited organic solutions were washed with water, 5% NaHCO₃ solution and water again, dried on MgSO₄, filtered and the solvent evaporated. A cream-white solid was isolated after recrystallization from methanol, m.p. 106-107°C (65% yield).⁷

IR Spectrum(CCl₄, cm⁻¹): 880 w, 980 w, 1020 w, 1150 m, 1180 m, 1195 s (C=O), 1450 m, 1480 w, 1730 vs (C=O), 2980 m, 3020 w.

¹³C NMR Spectrum (CDCl₃, ppm): 172.8 (C=O); 142.09 (C_{8a}); 140.38 (C_{4a}); 126.50 (C₂, C₆); 126.42 (C₃, C₇); 124.54 (C₄, C₈); 123.83 (C₁, C₅); 52.32 (CH₃); 47.88 (C₉, C₁₀); 46.73 (C₁₁, C₁₂).

Dihydrazide of trans 9.10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid⁵ (**2**)

An ethanolic solution of the ester **3** and hydrazide hydrate 85% in excess (molar ratio 1:8) was refluxed for 7 h.⁹ The solvent was evaporated in part and a cream solid was isolated by filtration. It was recrystallized from DMF, m.p. 275-276°C (75% yield).

IR Spectrum(KBr, cm⁻¹): 570 m, 745 m, 760 w, 920 w, 1020 m, 1220 w, 1250 w, 1350 w, 1470 w, 1515,m, 1600,s, 1640 vs (C=O), 2900-3050 m, 3320 vs (NH), 3350 s (NH).

Dipyrazole **4**

The hydrazide **2** was refluxed with an excess of diacetyl (molar ratio 1:2) in methylene chloride for 8 h in the presence of catalytic amount of HClO₄. After evaporation of the solvent a white solid (m.p. 233-4°C) was obtained by trituration with diethylether.

Elemental analysis Found(calculated): C 73.05 % (74.67 %), H 5.64 % (5.78 %), N 11.39 % (12.44%).

IR Spectrum(CCl₄, cm⁻¹): 701 w, 755 s, 768 m, 913 w, 939 w, 963 m, 1248 w, 1325 vs, 1342 s, 1381 vs, 1410 m, 1582 m, 1720 vs (C=O), 2907 w, 2971 w, 3024 w, 3070 w, 3101 w.

¹³C NMR Spectrum (CDCl₃, ppm): 172.61 (C=O), 151.34 (C=N), 144.0 (C-N), 142.48 (C_{8a}); 140.81 (C_{4a}); 126.19 (C₂, C₆); 126.05 (C₃, C₇); 125.44 (C₄, C₈); 123.51 (C₁, C₅); 52.32 (CH₃); 48.87 (C₉, C₁₀); 46.92 (C₁₁, C₁₂), 14.47 (CH₃), 13.45 (CH₃).

Complex **5**

An ethanolic solution of the dihydrazide **2**, acetylacetone and EuCl₃·6H₂O in molar ratio 2 : 2 : 1 was refluxed for 10 h in the presence of catalytic amount of HClO₄. After evaporation of the solvent a white solid (m.p. 203-5°C) was obtained.

Elemental analysis Found (calculated): C 46.12 % (46.97 %), H 4.64 % (4.40%), N 8.35 % (7.82 %), Cl 9.21 % (9.92 %).

IR Spectrum: 703w, 753s, 761m, 912m, 937m, 962s, 1248m, 1321vs, 1341m, 1376s, 1408w, 1582m, 1717 vs (C=O), 2914w, 3267w.

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