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Synthesis, Biophysical Studies and Antiproliferative Activity of Platinum(II) Complexes Having 1,2-Bis(amino methyl)carbobicyclic Ligands

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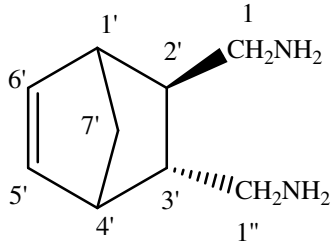
SYNTHESIS AND SPECTROSCOPIC CHARACTERIZATION OF DIAMINES (1) TO (6)

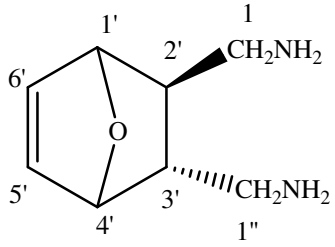
General procedure. The precursory dinitrile (resulting from the Diels-Alder reaction of cyclopentadiene and fumaronitrile) (963 mg, 7 mmol) was dissolved in diethyl ether (30 mL) and added dropwise to a suspension of $LiAlH_4$ (1.02 g, 26.8 mmol) in ether (10 mL). After 2 h of stirring at room temperature, quenching of the hydride was performed by cautious dropwise addition of 2 mL of water, 4 mL of 30 % NaOH and 5 mL of water. The solutions were filtered off and the solvent eliminated at vacuum, obtaining the bicyclic diamine **1** as yellow oil. (788 mg, 92% yield).



1

(3-aminomethyl-bicyclo[2.2.1]hept-5-ene-2-yl)-methylamine (1)
IR (film) 3286, 3056, 2959, 2871, 1576. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91-1.00 (1H, m, H-7a' or H-7b'), 1.35-1.55 (7H, m, 4NH, H-2', H-3', H-7a' or H-7b'), 2.35-2.55 (2H, m, H-1', H-4'), 2.62-2.91 (4H, m, H-1, H-1''), 6.02 (1H, dd, J_1 = 3 Hz, J_2 = 5.8 Hz, H-5' or H-6'), 6.19 (1H, dd, J_1 = 3.4 Hz, J_2 = 5.3 Hz, H-5' or H-6'). ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.2 (C-2' or C-3'), 44.9 (C-2' or C-3'), 45.9 (C-7' or C-1 or C-1''), 46.3 (C-7' or C-1 or C-1''), 47.3 (C-7' or C-1 or C-1''), 48.0 (C-1' or C-4'), 48.7 (C-1' or C-4'), 133.3 (C-5' or C-6'), 137.7 (C-5' or C-6'). MS (CI, %) 134 (2, M- NH_4^+), 153 (100, M+H^+), 154 (10, M+2H^+). Anal. Calcd. for $C_9H_{16}N_2$: C, 71.01; H, 10.59; N, 18.40. Found: C, 71.06; H, 10.62; N, 18.39.

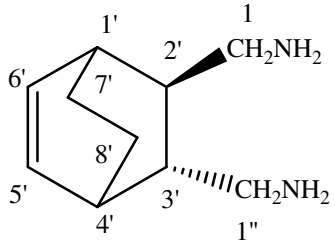
(3-aminomethyl-7-oxa-bicyclo[2.2.1]hept-5-ene-2-yl)-methylamine (3)
Reaction was carried out on a similar way than in the previous section but using THF as a solvent. The product was isolated after purification by column chromatography (77 mg, Y = 36 %, eluted with EtOH/NH_3 8:2).



3

Yellowish oil, IR (film) 3349, 3320, 3200, 3100, 3075, 2990, 2921, 2880, 1574. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.13-1.26 (1H, m, H-2'), 1.3-1.65 (2H, m, NH), 1.7-1.88 (1H, m, H-3'), 2.53 (2H, dd, J_1 = 5.8 Hz, J_2 = 6.0 Hz, H-1 or H-1''), 2.85 (2H, dd, J_1 = 1.7 Hz, J_2 = 7.1 Hz, H-1 or H-1''), 4.68-4.73 (1H, m, H-1' or H-4'), 4.96 (1H, dd, J_1 = 0.6 Hz, J_2 = 3.8 Hz, H-1' or H-4'), 6.32 (1H, dd, J_1 = 1.5 Hz , J_2 = 5.9 Hz, H-5' or H-6'), 6.44 (1H, dd, J_1 = 1.9 Hz , J_2 = 5.9 Hz, H-5' or H-6'). ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.8 (C-1 or C-1''), 45.7 (C-1 or C-1''), 47 (C-2' or C-3'), 47.6 (C-2' or C-3'), 79.9 (C-1' or C-4'), 81 (C-1' or C-4'), 133.1 (C-5' or C-6'), 136.5 (C-5' or C-6'). MS (CI, %) 155 (100, $M+H^+$), 156 (12, $M+2H^+$), 157 (5, $M+3H^+$), 172 (4, $M+NH_4^+$), 309 (5, $2M+H^+$). Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.36; H, 9.12; N, 18.20.

(3-aminomethyl-bicyclo[2.2.2]oct-5-ene-2-yl)-methylamine (5)



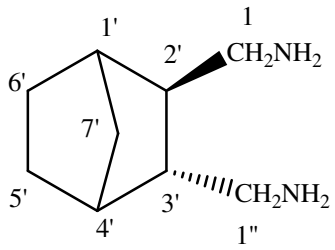
5

Yellowish oil. Y = 88 %. IR (film) 3291, 3040, 2938, 2867, 1576. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92-1.23 (3H, m, H-7', H-8a'), 1.18-1.26 (6H, m, 4NH, H-8b', H-2'), 1.28-1.44 (1H, m, H-3'), 2.39 (1H, s, H-1' or H-4'), 2.43 (1H, s, H-1' or H-4'), 2.45-2.56 (2H, m, H-1a, H-1a''), 2.65 (1H, dd, J_1 = 8.7 Hz, J_2 = 12.7 Hz, H-1b or H-1b''), 2.79 (1H, dd, J_1 = 6.3 Hz, J_2 = 12.5 Hz, H-1b or H-1b''), 6.09-6.29 (1H, m, H-5' or H-6'), 6.3-6.39 (1H, m, H-5' or H-6'). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.8 (C-7' or C-8'), 25.7 (C-7' or C-8'), 31.2 (C-1' or C-4'), 32.4 (C-1' or C-4'), 45.5 (C-2' or C-3'), 45.7 (C-2' or C-3'), 48 (C-1 or C-1''), 48.01 (C-1 or C-1''), 132 (C-5' or C-6'), 136.5 (C-5' or C-6'). MS (CI, %) 167 (100, $M+H^+$). Anal. Calcd. for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91; N, 16.85. Found: C, 72.28; H, 10.87; N, 18.79.

Synthesis of the saturated diamines (2), (4) and (6)

These saturated diamine ligands were obtained, from the precursory dinitrile Diels-Alder cycloadducts, by hydrogenation (of the C=C bond) using H_2 / Pd-C under standard conditions and in quantitative yield, followed by reduction of the dinitrile functionalities with $LiAlH_4$ under the before-described conditions. The yield of the furan derived diamine resulted lower than in the other two cases due to the low stability of the cycloadduct which is inclined to give retro-Diels-Alder reactions.

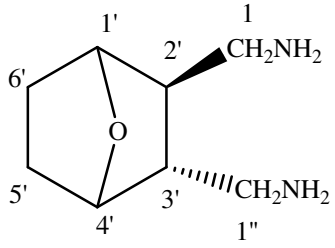
(3-aminomethyl-bicyclo[2.2.1]hept-2-yl)-methylamine (2)



2

Yellowish oil. Y = 94 % . IR (film) 3322, 2948, 2875, 1564. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (1H, d, J = 8.1 Hz, H-7a'), 1.10-1.25 (3H, m, H-7b', H-2', H-3'), 1.31-1.51 (4H, m, H-5', H-6'), 2.05-2.06 (1H, m, H-1' or H-4'), 2.26-2.28 (1H, m, H-1' or H-4'), 2.46-2.46 (1H, m, H-1a or H-1a''), 2.62-2.81 (3H, m, H-1a or H-1a'', H-1b , H-1b''), 2.9-3.2 (4H, m, 4NH). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 22.0 (C-5' or C-6'), 30.1 (C-5' or C-6'), 37.0 (C-7'), 38.8 (C-2' or C-3'), 39.8 (C-2' or C-3'), 43.5 (C-1 or C-1''), 46.5 (C-1 or C-1''), 49.5 (C-1' or C-4'), 51.6 (C-1' or C-4'). MS (CI, %) 155 (100, M+H$^+$), 172 (10, M+NH_4^+). Anal. Calcd. for $C_9H_{18}N_2$: C, 70.08; H, 11.76; N, 18.16. Found: C, 70.12; H, 11.80; N, 18.19.

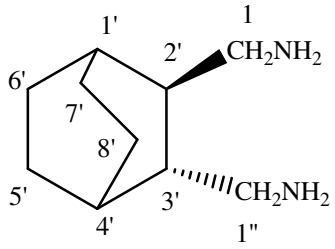
(3-aminomethyl-7-oxa-bicyclo[2.2.1]hept-2-yl)-methylamine (4)



4

Yellowish oil. IR (film) 3250, 3150 (N-H, st), 2965, 2921, 1655. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3-1.5 (2H, m, H-5' or H-6'), 1.6-1.7 (2H, m, H-5' or H-6'), 1.7-1.88 (2H, m, H-2', H-3'), 2.5-2.8 (2H, m, H-1 or H-1''), 2.8-2.9 (2H, m, H-1 or H-1''), 4.3 (1H, d, J_1 = 5.1 Hz, H-1' or H-4'), 4.5-4.6 (1H, m, H-1' or H-4'). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (C-5' or C-6'), 30.1 (C-5' or C-6'), 42.1 (C-1 or C-1''), 44.9 (C-1 or C-1''), 50.8 (C-2' or C-3'), 52.2 (C-2' or C-3'), 78.5 (C-1' or C-4'), 79.5 (C-1' or C-4'). M S (CI, %) 138 (13, M-NH_4^+), 157 (100, M+H$^+$), 158 (11, M+2H$^+$), 167 (4). Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.93. Found: C, 61.57; H, 10.29; N, 18.01.

(3-aminomethyl-bicyclo[2.2.2]octane-2-yl)-methylamine (6)



6

Yellowish oil. Y = 81 % .IR (film): 3290, 2950, 2860, 1650, 1550. ^{1}H NMR (200 MHz, $CHCl_3$) δ: 1.16 (2H, dd, J_1 = 6.2 Hz, J_2 = 12.4 Hz, H-7' or H-8'), 1.31-1.74 (10H, m, H-1', H-2', H-3', H-4', H-5', H-6', H-7' or H-8'), 2.51-2.93 (2H, m, H-1 or H-1''), 2.95-3.24 (2H, s, H-1 or H-1''). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4 (C-5' or C-6' or C-7' or C-8'), 26.5 (C-5' or C-6' or C-7' or C-8'), 26.9 (C-5' or C-6' or C-7' or C-8'), 27.1 (C-5' or C-6' or C-7' or C-8'), 27.2 (C-1' or C-4'), 27.3 (C-1' or C-4'), 45.7 (C-2' or C-3'), 45.8 (C-1 or C-1''), 45.9 (C-2' or C-3'), 51.6 (C-1 or C-1''). MS (CI, %) 169 (100, $M+H^+$). Anal. Calcd. for $C_{10}H_{20}N_2$: C, 71.37; H, 10.98; N, 16.65. Found: C, 71.34; H, 11.01; N, 16.70.

TABLE OF ELEMENTAL ANALYSES OF COMPLEXES 7 TO 12

Complex	Formula	Calculated (%)			Found (%)		
		C	H	N	C	H	N
7	$C_9H_{16}N_2Cl_2Pt$	25.85	3.86	6.70	25.80	3.82	6.71
8	$C_9H_{18}N_2Cl_2Pt$	25.71	4.28	6.66	25.93	4.54	6.39
9	$C_8H_{14}ON_2Cl_2Pt$	22.87	3.36	6.67	23.15	3.77	6.16
10	$C_8H_{16}ON_2Cl_2Pt$	22.76	3.82	6.63	23.46	4.25	6.31
11	$C_{10}H_{18}N_2Cl_2Pt$	27.79	4.20	6.48	27.61	4.57	6.13
12	$C_{10}H_{20}N_2Cl_2Pt$	27.66	4.64	6.45	27.68	5.05	6.16