SYNTHESES OF *N*-SUBSTITUTED 2,5-PIPERAZINDIONES

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Abstract- The synthesis of 2,5-piperazindiones, 1,6-dimethoxycarbonylmethyl-2,5-piperazindione (**1a**), 1,6-di-α-methylbenzylcarboxamidomethyl-2,5-piperazindione (**1b**), 1,6-dibenzhydrylcarboxamidomethyl-2,5-piperazindione (**1c**) and 1,6-di-2-(1-phenylbenzimidazolyl)methyl-2,5-piperazindione (**1d**), is reported. The cyclic dipeptide (**1a**) was obtained from the auto-condensation of the dimethyliminodiacetate promoted by triethylborane or triphenylsilane. Compounds (**1b-1d**) were prepared by refluxing iminodiacetic acid and the corresponding amine. The X-Ray diffraction structure of (**1a**) reveals boat conformation for its 2,5-piperazindione ring.

The 2,5-piperazindiones (2,5-PPD) are cyclic dipeptides of *cis* structure (**1**) (Figure 1). They are found in nature as degradation products of proteins, peptides and polypeptides,[1,2] and moreover in antibiotics[3] as bicyclomycine (**2**),[4] and in antitumorals as 3,6-di(5-chloro-2-piperidyl)piperazin-2,5-dione (**3**).[5] They are used in asymmetric synthesis of α-amino acids[6,7] and are formed by cyclization of linear dipeptides,[7] dimerization of α-amino esters[8,10] or Diels-Alder reactions.[11] Their rigid structures make them excellent model for structural studies in proteins.[9,12,13] The ring conformation depends on the substituents,[14,16] it can be planar, boat or twisted boat.[15] Some metallic complexes of 2,5-piperazindiones are important in biological systems, the 2,5-piperazindiones derived form histidine (**4**) catalyzes the oxidation of L-DOPA [3-(3,4-dihydroxyphenyl)alanine] and the addition of Cu^{2+} increases the rate of oxidation.[17] The

rhodotorulic acid (**5**) forms metallic complexes with Fe(III) and Cr(III).[18,19] Compound (**5**) is involved in the iron transport of *Rhodotorula pilimanae*.[20]

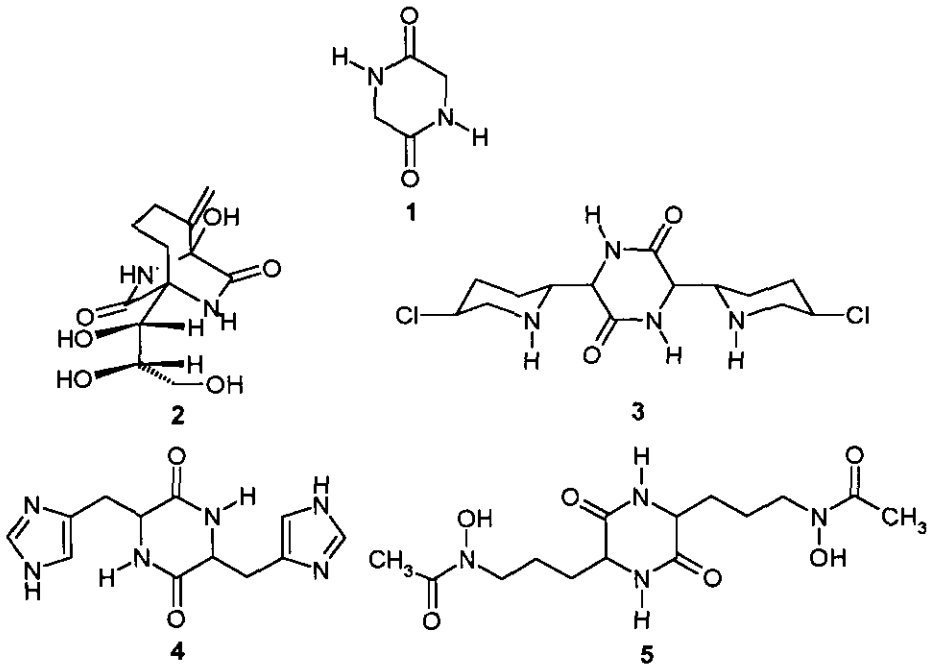
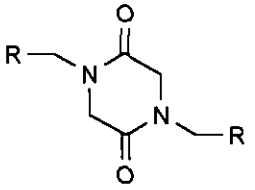


Figure 1

Iminodiacetic acid and its derivatives may dimerize to give N-substituted 2,5-piperazindiones (**1**). Only a few examples of these *N*-substituted heterocycles are reported.[21] Their synthesis give low yields, and purification is difficult.[21,22] Moreover no X-Ray diffraction structures of *N*-substituted 2,5-piperazindiones have been described. We report here the synthesis of 2,5-piperazindiones (**1a-1d**) and the X-Ray diffraction structure of the piperazindione (**1a**).



1a R = $COOCH_3$
1b R = $CONHCH(CH_3)C_6H_5$
1c R = $CONHCH(C_6H_5)_2$
1d R = 2[1-phenylbenzimidazole]

Figure 2

RESULTS AND DISCUSSION.

The most convenient way to prepare 2,5-piperazindiones is the condensation of amino acids or its esters. We have now found that also dimethyl iminodiacetate (**6**) on standing slowly dimerizes to (**1a**). This reaction can be promoted by the action of Lewis acids such as triethylborane or triphenylsilane. Thus, compound (**1a**) was synthesized by refluxing in toluene dimethyl iminodiacetate (**6**) with one equivalent of triethylborane (50 % yield). The same result was found when the reaction was performed with triphenylsilane (Figure 3). Compound (**1a**) was purified form CCl_4 solution by precipitation with hexane.

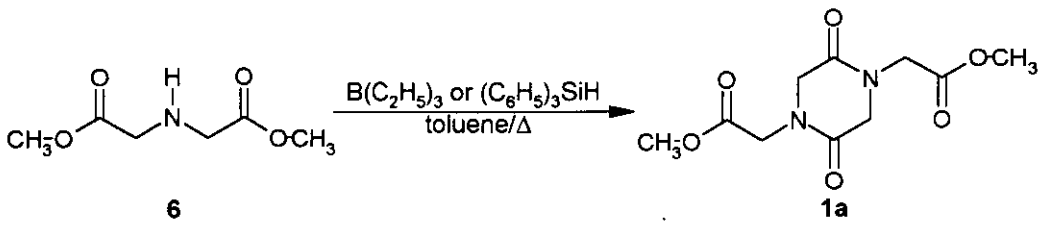


Figure 3

Heterocycles (**1b-1d**) were prepared from the equimolar reaction of iminodiacetic acid (**7**) and the corresponding amine (Figure 4). They precipitate from the mixture, and were filtered and washed with CH_2Cl_2. The reaction of **7** with α-methylbenzylamine produces compound (**1b**) (16 %). In contrast, the reaction with three equivalents of amine affords the diamide (**8**) (75 %).[29] The 2,5-piperazindiones (**1c**) (11 %) and (**1d**) (8 %) were purified by dissolving the reaction product in ethyl acetate and precipitation with hexane.

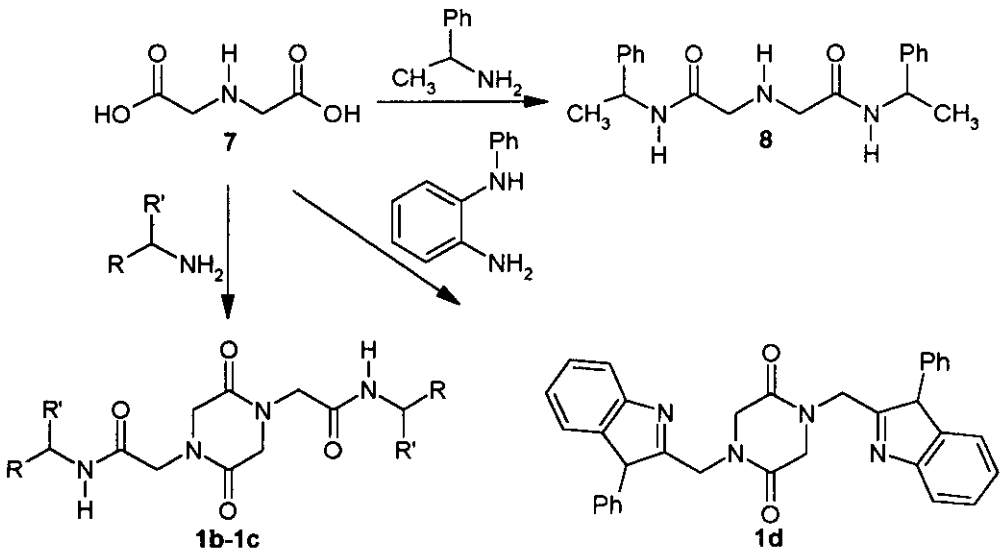


Figure 4

Molecular structure of (1a) obtained by X-Ray diffraction.

Single crystals of the 2,5-piperazindione (**1a**) were obtained, they are monoclinic and the space group was determined as $P2_1/a$. The X-Ray diffraction analysis lead to a molecular structure of compound (**1a**) which shows the boat conformation for the 2,5-piperazindione ring system (Figure 5). The dihedral angle between the planes of the amide groups is 166.2°. It was established that the glycine dipeptide is planar,[23,24] but a bulky group bonded to the ring may change this conformation.[8,13,25] The tricoordinated nitrogen atoms are in a planar environment. The two ester groups are oriented to the same ring face, with the oxygen atoms pointing to H22 and H52. The calculated distance between O11 and H22 is 2.71(4) Å, and between O16 and H52 is 2.58(4) Å, close to the van der Waals radii (2.70 Å). The dihedral angles

N1-C9-C10-O11 and N4-C14-C15-O16 are -16°. Bond lengths and angles of **1a** are in Tables 1 and 2 and crystallographic data and coordinates are summarized in Tables 3 and 4.

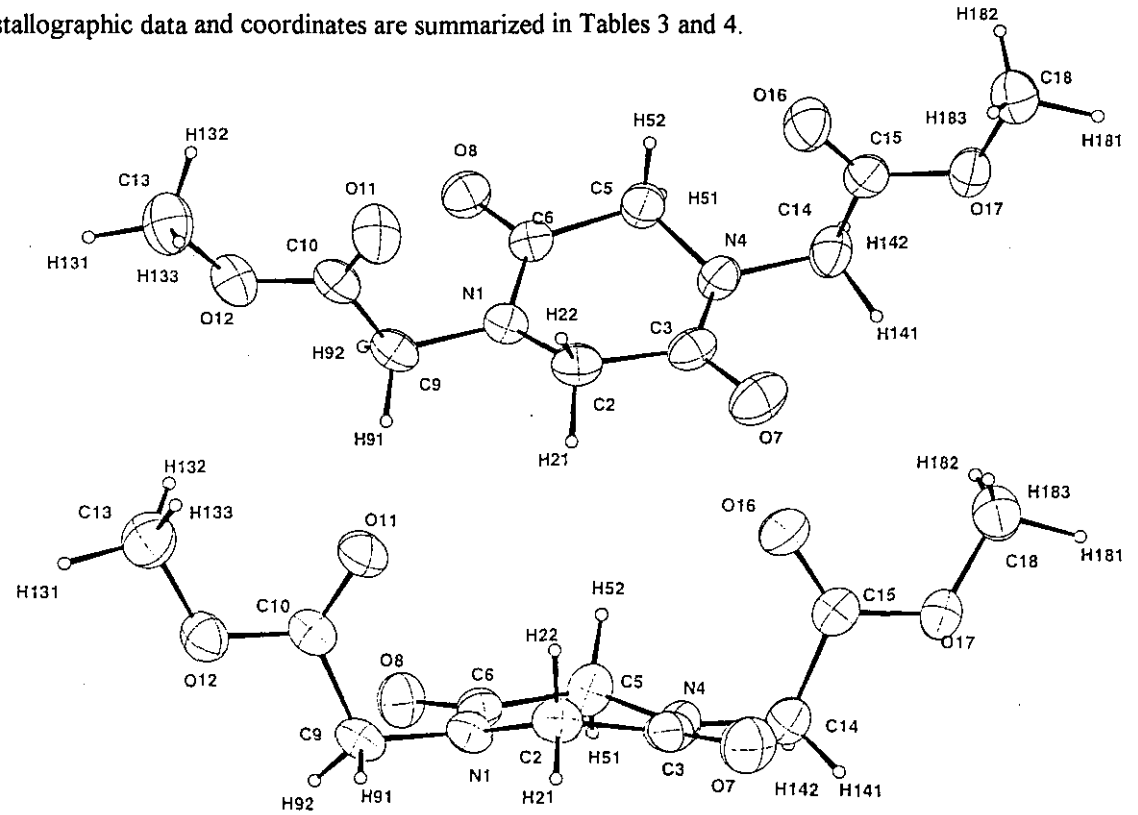


Figure 5. Front and lateral views of the X-Ray diffraction structure of compound (**1a**).

Table 1. Interatomic Distances (Å).

N1-C2	1.450(4)	N1-C6	1.346(4)
N1-C9	1.455(4)	N4-C3	1.350(4)
N4-C5	1.459(4)	N4-C14	1.450(4)
O7-C3	1.223(4)	O8-C6	1.227(3)
O11-C10	1.184(3)	O12-C10	1.335(4)
O12-C13	1.444(5)	O16-C15	1.206(3)
O17-C15	1.318(4)	O17-C18	1.453(5)
C2-C3	1.506(5)	C5-C6	1.492(4)
C9-C10	1.503(4)	C14-C15	1.501(5)
H52-O16	2.577(3)	H22-O11	2.713(3)
H141-O7	2.446(3)	H92-O8	2.453(3)

Analysis of the more stable conformer of **1a** by molecular mechanic calculations (MM2) gives a similar structure. When the two chains are oriented through opposed faces the structure has higher energy. The chair conformation is not favored in these heterocycles.

In solution the ^{1}H and ^{13}C NMR spectra of **1a-1b** show that they are in conformational equilibrium. In the ^{1}H NMR spectra the methylene signals are singlets. The NMR spectra at -55 °C did not show any

change. The unequivocal assignment of the ^{1}H and ^{13}C NMR signals of exo- and endocyclic methylene and carbonyl groups was performed with HETCOR and FLOCK experiments. In the ^{1}H coupled ^{13}C NMR spectrum of **1b** the endocyclic carbonyl groups signals are triplets owing to the coupling with the nearest methylene groups, the exocyclic carbonyl have a higher multiplicity by additional coupling with N-H groups. Assignment of the ^{13}C NMR spectrum of **1b** was made by comparison with that of *N*-phenyl-benzimidazole.[26]

Table 2. Bond Angles (deg).

C2-N1-C6	122.5(3)	C2-N1-C9	117.8(3)
C6-N1-C9	117.3(3)	C3-N4-C5	122.2(3)
C3-N4-C14	118.5(3)	C5-N4-C14	116.9(3)
C10-O12-C13	116.6(3)	C15-O17-C18	116.6(3)
N1-C2-C3	115.1(3)	N4-C3-O7	122.0(3)
N4-C3-C2	118.1(3)	O7-C3-C2	119.9(3)
N4-C5-C6	115.7(3)	N1-C6-O8	122.6(3)
N1-C6-C5	118.3(3)	O8-C6-C5	119.1(3)
N1-C9-C10	111.5(3)	O11-C10-C12	124.1(3)
O11-C10-C9	124.6(3)	O12-C10-C9	111.3(3)
N4-C14-C15	112.4(3)	O16-C15-O17	125.0(3)
O16-C15-C14	124.4(3)	O17-C15-C14	110.6(3)

EXPERIMENTAL

All solvents were freshly distilled. Melting points were measured on a Gallenkamp apparatus and are uncorrected. The IR spectra were taken in KBr discs using a Perkin Elmer 16F PC IR spectrophotometer. The NMR data were obtained on a JEOL (270 MHz) in $CDCl_3$, DMSO-d_6, and D_2O. ^{1}H and ^{13}C NMR spectra were measured with TMS as internal reference. MS spectra were obtained on a Hewlett-Packard HP 5989A. Elemental Analyses were performed in a Sisson Ea-1108 (CHNS-O) apparatus.

Table 3. Crystallographic data of compound (**1a**).

Formula, $C_{10}H_{14}N_2O_6$	F.W. 258.23
Space group, $P2_1/a$	a(Å), 10.7424(2)
b(Å), 9.2218(3)	c(Å), 12.7132(5)
Z, 4	BETA(°), 106.395(2)
d calcd, g cm^{-3}, 1.416	Volumen ($Å^3$), 1208.2(6)
Scan type, $\omega/2\theta$	(MoKα), λ, 0.71069 Å
Diffractometer, CAD4-Enraf-Nonius	θ Range (°), 2.06-27
No. of unique reflections, 2621	Scan width (°), 0.43 + 0.60 tgθ
R, 0.042	No. of reflections collected, 2946
Marging R. Factor, 0.898	No. of reflections with I>3σ I, 1346
Goodness of fit 2.37	Rw, 0.038
$\Delta\rho$min(e/A^3) -0.17	No. of Variables, 206
$\Delta\rho$max(e/A^3) 0.042	

1,6-Dimethoxycarbonylmethyl-2,5-piperazindione (1a). A solution of 1.0 g (6.2 mmol) of dimethyl iminodiacetate (**6**) in 75 mL of toluene was treated with 0.9 mL (6.2 mmol) of triethylborane or 1.61 g (6.20 mmol) of triphenylsilane at rt. The reaction mixture was refluxed for 48 h. The solvent was evaporated at reduced pressure. A solid was obtained which was purified by precipitation from CCl_4 with hexane (0.43 g, 54 %). mp 198-201 °C; IR (KBr, ν_{max}/cm^{-1}), 2990, 2956, 2932, 2840 (C-H), 1746, 1680 (C=O), 1474, 1436 (CH_2), 1372 (CH_3), 1222 (C-O-C); ^1H (270 MHz, DMSO-d_6), δ 3.67 (s, 6H, CH_3), 4.09 (s, 4H, endo CH_2), 4.15 (s, 4H, exo CH_2); ^{13}C (67.8 MHz, DMSO-d_6), δ 46.5 (exo CH_2), 50.1 (endo CH_2), 52.0 (CH_3), 164.3 (endo C=O), 168.8 (exo C=O); MS (EI, 70 ev) m/z, 259 (3), M^+ 258 (21), 227 (5), 226 (11), 199 (11), 198 (13), 171 (25), 102 (25), 43 (18), 42 (100); Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.01; H, 6.00; N, 12.41.

Table 4. Crystallographic coordinates of compound (**1a**).

Atom	x/a	y/b	z/c	U(iso)
N(1)	0.7182(2)	0.1642(3)	0.1026(2)	0.0458
N(4)	0.7672(2)	0.1070(3)	0.3251(2)	0.0524
O(7)	0.6483(2)	-0.0973(3)	0.2892(2)	0.0738
O(8)	0.8257(2)	0.3769(2)	0.1388(2)	0.0595
O(11)	0.4987(2)	0.3105(3)	-0.0158(2)	0.0687
O(12)	0.5892(2)	0.3529(3)	-0.1506(2)	0.0601
O(16)	0.6085(2)	0.2222(3)	0.4431(2)	0.0666
O(17)	0.7034(2)	0.0821(2)	0.5865(2)	0.0619
C(2)	0.6433(3)	0.0519(4)	0.1367(3)	0.0531
C(3)	0.6872(3)	0.0139(4)	0.2565(3)	0.0522
C(5)	0.7954(4)	0.2511(4)	0.2905(3)	0.0548
C(6)	0.7805(3)	0.2688(3)	0.1710(2)	0.0454
C(9)	0.6952(3)	0.1893(4)	-0.0141(3)	0.0515
C(10)	0.5830(3)	0.2904(4)	-0.0575(3)	0.0474
C(13)	0.4813(4)	0.4440(6)	-0.2052(4)	0.0774
C(14)	0.7959(4)	0.0817(5)	0.4418(3)	0.0607
C(15)	0.6914(3)	0.1376(3)	0.4888(3)	0.0512
C(18)	0.6127(5)	0.1331(5)	0.6444(4)	0.7680

1,6-Di-α-methylbenzylcarboxamidomethyl-2,5-piperazindione (1b). 4.14 g (31.12 mmol) of iminodiacetic acid (**7**) was refluxed for 3 days in 3.77 g (31.12 mmol) of *R*-(+)-α-methylbenzylamine, in this period a solid precipitated. The solid was filtered and washed with CH_2Cl_2 and dried at reduced pressure to give a white solid (1.52 g, 16 %). mp 218-220 °C, $[\alpha]^{29}$ = +165.25°(c = 1.05, MeOH), IR (KBr, ν_{max}/cm^{-1}), 3302, 3290 (N-H), 3000, 2973, 2965 (C-H), 1663, 1651 (C=O), 1558 (N-H), 1483 (CH_2), 1372 (CH_3), 1296 (N-H), 750, 698 (C-H); ^1H (90 MHz, DMSO-d_6), δ 1.36 (d, *J* = 7.25 Hz, 6H, CH_3), 4.06 (s, 4H, exo CH_2), 4.09 (s, 4H, endo CH_2), 4.93 (q, *J* = 7.2 Hz, = 7.9 Hz, 2H, CH), 7.21-7.53 (m, 10H, Ph), 8.65 (d, *J* = 7.9 Hz, 2H, NH); ^{13}C (67.80 MHz, DMSO-d_6), δ 22.37 (CH_3), 47.7 (exo CH_2),

47.9 (endo CH_2), 125.9 (C-*o*), 126.6 (C-*p*), 128.24 (C-*m*), 144.3 (C-*i*), 164.1 (endo C=O), 166.3 (exo C=O); MS (EI, 70 ev) m/z; M^+ 436 (1), 120 (93), 106 (19), 105 (100), 77 (22), 44 (17), 43 (20), 42 (100), 28 (34); Anal. Calcd. for $C_{24}H_{28}N_4O_4$: C, 66.04; H, 6.46; N, 12.83. Found. C, 66.03; H, 6.51; N, 13.11.

1,6-Dibenzhydrylcarboxamidomethyl-2,5-piperazindione (1c). 2.5 g (19 mmol) of iminodiacetic acid (7) was refluxed for 3 days with a one equivalent (3.5 g) of *N*-phenylbenzylamine. A solid was formed which was filtered off, the reaction product was washed with CH_2Cl_2 and dried at reduced pressure to give a white solid, the piperazindione was purified by precipitation with ethyl acetate/hexane. (1.0 g, 11 %). mp 266-269 °C, IR (KBr, ν_{max}/cm^{-1}), 3061, 3031, 2967, 2928, 2892 (C-H), 1677, 1638 (C=O), 1541 (N-H), 1480 (CH_2), 1330 (CH_3), ^1H (270 MHz, DMSO-d_6), δ 4.06 (s, 4H, exo CH_2), 4.09 (s, 4H, endo CH_2), 6.12 (d, J = 8.6 Hz, 2H, CH), 7.20-7.36 (m, 20 H, Ph), 9.00 (d, J = 8.6 Hz, 2H, NH); ^{13}C (67.80 MHz, DMSO-d_6), δ 47.7 (exo CH_2), 50.7 (endo CH_2), 56 (CH), 127.0 (C-*p*), 127.3 (C-*o*), 128.4 (C-*m*), 142.2 (C-*i*), 164.1 (exo C=O), 166.7, (endo C=O). Anal. Calcd. For $C_{34}H_{32}N_4O_4$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.09; H, 6.12; N, 10.06.

1,6-Di-2-phenylbenzimidazolylmethyl-2,5-piperazindione (1d). A mixture of 3.61 g (27.1 mmol) of iminodiacetic acid (7) was refluxed for 9 h in 10.0 g (54.3 mmol) of *N*-phenyl-1,2-phenylenediamine. Then 200 mL of ethanol and 12.0 g of deactivated carbon was added. The mixture was refluxed for 2 h and was hot filtered. The solvent evaporated under vacuum. **1d** was purified by dissolving the solid residue in ethyl acetate and precipitating it with hexane. **1a** was obtained as a beige solid (0.58 g, 8 %). mp 305-306 °C; IR (KBr, ν_{max}/cm^{-1}), 3060, 2924, 2856 (C-H), 1672 (C=O), 1500, 1476 (CH_2), 1332, 1296 (C-N); ^1H (270 MHz, $CDCl_3$), δ 3.98 (s, 4H, exo CH_2), 4.70 (s, 4H, endo CH_2), 7.10-7.48 (m, 18H, Ph); ^{13}C (22.49 MHz, $CDCl_3$), δ 42.1 (exo CH_2), 49.7 (endo CH_2), 110.0 (C-7), 119.0 (C-4), 122.8 (C-5), 123.5 (C-6), 126.9 (C-*o*), 129.2 (C-*p*), 130.0 (C-*m*), 134.8 (C-8), 136.6 (C-*i*), 142.1 (C-9), 147.9 (C-2), 163.1 (C=O); MS (EI, 70 ev) m/z, M^+ 526 (5), 208 (42), 207 (50), 206 (14), 55 (10), 44 (19), 43 (18), 32 (15), 29 (15), 28 (100); Anal. Calcd. for $C_{23}H_{26}N_6O_2$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.01; H, 5.15, N, 16.16.

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