Synthesis of 8,9-Dihydrodipyrazolo[3,4-*b*:4',3'-*f*][1,5]Diazocin-10(1*H*)-one. A New Ring System

Onofrio Migliara*, Liliana Lamartina, Marina Timoneri and Salvatore Plescia

Dipartimento di Chimica e Tecnologie Farmaceutiche dell'Università,
Via Archirafi, 32-90123 Palermo, Italy

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8,9-Dihydrodipyrazolo[3,4-*b*:4',3'-*f*][1,5]diazocin-10(1*H*)-ones **7** were prepared by cyclization of 1-ethyl-*N*,3-dimethyl-4-acetamido-*N*-(1-R_1-3-R_2-1*H*-pyrazol-5-yl)-1*H*-pyrazole-5-carboxamides **6** by a Bischler-Napieralski cyclization. A complete assignment of the chemical shifts to the carbon atoms of compound **7** was performed by different nmr experiments, such as DEPT and XHDEPT for one-bond C-H correlations and COLOC experiments for long-range C-H correlations.

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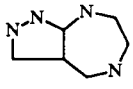
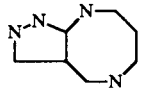
Introduction.

In a previous paper, we reported the synthesis of pyrazolodiazepine derivatives of type **I** and their activity on CNS [1-2]. Also pyrazolodiazocines of type **II** have shown to be active on CNS [3].



I



II

Furthermore, 1,5-benzodiazocines have acquired considerable importance because of their interesting analgesic, anti-inflammatory, anticonvulsant, tranquilizer activities [4-6]. In connection with our investigation on the pyrazole series with potential pharmaceutical and microbiological properties [7-10], we became interested in the synthesis of derivatives of the novel ring system: 8,9-dihydrodipyrazolo[3,4-*b*:4',3'-*f*][1,5]diazocin-10(1*H*)-one, by the Bischler-Napieralski cyclization reaction on 1-ethyl-*N*,3-dimethyl-4-acetamido-*N*-(1-R_1-3-R_2-1*H*-pyrazol-5-yl)-1*H*-pyrazole-5-carboxamides **6a-d**.

Thus the reaction of 5-pyrazolecarbonyl chloride **1** (Scheme 1) with the aminopyrazoles **2a-d**, gave, in moderate yields (70-75%), 5-pyrazolamides **3a-d**, key intermediates in the synthesis of the tricyclic system **7**. Spectroscopic data (ir, nmr) of **3** were in accord with the assigned structure. The ^1H and ^{13}C nmr chemical shifts of these compounds are reported in Table 1. The assignment of the chemical shifts in the fully proton decoupled ^{13}C nmr spectra of the all compounds was made on the ground of both known substituent effects and DEPT-135 experiments and confirmed by ^{13}C-^1H heterocorrelated spectra which provided for both one-bond and long-range C-H interactions [11]. The action of dimethyl sulfate on products **3a-d** afforded the corresponding compounds **4a-d**; in fact, compound **4a**, taken as an example, by alkaline hydrolysis gave the derivative **8a**, that was identical in all the respects with an authentic sample of 5-methylamino-1-phenylpyrazole [12]. Catalytic hydrogenation on Raney-nickel of products **4** led to the intermediates **5a-d** that were not characterized, but, directly converted to **6a-d** by the reaction with acetic anhydride.

The nmr spectra in deuteriodimethyl sulfoxide solutions of both **4** and **6** were in accord with the assigned structures (Table 1), and provided evidence for the presence of rotational isomerism due to the partial double bond character of the C-N bond. In fact, double signals for each carbon atom in ^{13}C-nmr spectra gave an account of the relative abundances of the two conformers (55-75% for the more abundant isomer). Thus two signals appeared for the NCH_3 carbon atom, the upfield one being more abundant in all derivatives. According to the literature [13] the upfield resonance was assigned to the conformer bearing the methyl group *syn* to the carbonyl. Also the carbonyl carbon resonance of the more abundant conformer resulted in an upfield shift with respect to the corresponding isomer. Finally, compounds **6a-d** were converted into **7a-d** by the Bischler-Napieralski reaction. The structure of **7a-d** was assigned as 1-ethyl-3,5,9-trimethyl-8-R_1-6-R_2-8,9-dihydrodipyrazolo[3,4-*b*:4',3'-*f*][1,5]diazocin-10(1*H*)-one, on the basis of elemental analysis and spectroscopic data. The proton nmr spectra of **7a-d** in deuteriodimethyl sulfoxide solution (Table 2) showed the signals of the ethyl group at N-1, the singlets of the methyl groups at C-3, C-5 and N-9 and the signals of the protons of R_1 and R_2 substituents.

Analogously, in the ^{13}C nmr of **7a-d** we found the signals of the quaternary carbon atoms C-3, C-3a, C-5a, C-8a, C-10a, and CO, together with the signals of the carbon atoms of the R_1 substituents. Furthermore, **7a** and **7c** exhibited a signal of a carbon bearing a proton for the C-6, whereas the signal of this carbon atom corresponded to a quaternary carbon in **7b** and **7d** accompanied the signal of the methyl group at C-6. Particularly, in the proton spectra of compounds **7**, the disappearance of the signals of both pyrazole H-4' and amide NH observed in the compounds **6**; together with the relevant downfield shift (Table 2) of the signals of C-4 and C-4' of the pyrazole

Scheme 1

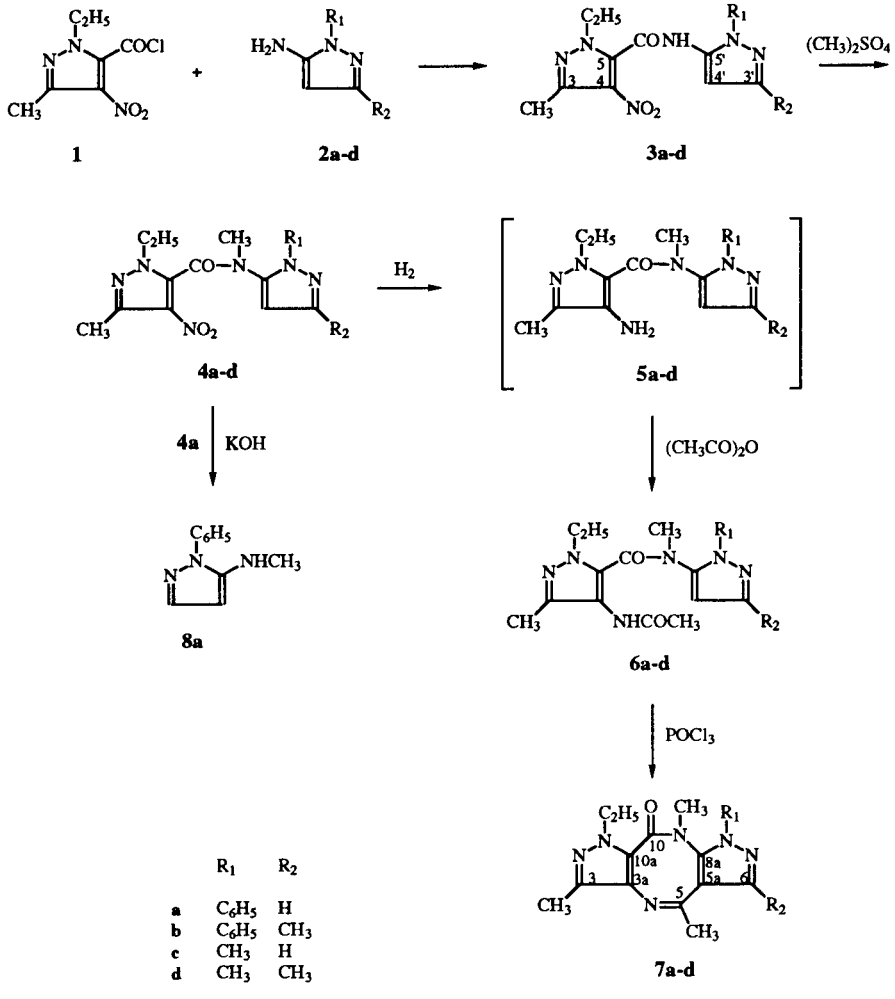


Table 1

^{13}C-and ^{1}H-NMR Chemical Shift Values of Compounds **3-6** [a]

	3a	**3b**	**3c**	**3d**	**4a**	**4b**	**4c**	**4d**	**6a**	**6b**	**6c**	**6d**
C-3	144.3	144.4	144.4	144.4	144.3 (145.1)	144.2 (145.1)	144.6 (145.1)	144.7 (145.2)	138.9 (141.1)	139.2 (141.1)	140.2 (141.2)	140.4 (141.2)
C-4	130.0	130.1	130.3	130.3	129.4 (129.6)	129.5 (129.7)	129.1 (129.7)	129.4 (129.9)	115.8 (116.6)	115.8 (116.6)	116.2 (116.6)	116.2 (116.6)
C-5	136.2	136.4	136.2	136.3	134.2 (135.0)	134.3 (135.1)	135.9 (135.4)	136.1 (135.6)	128.5 (129.0)	128.6 (129.1)	129.6 (129.6)	129.6 (129.6)
C-3'	140.0 7.8	148.5	137.8 7.4	146.0	140.2 7.7 (140.1) (7.8)	148.4	138.3 7.3 (138.0) (7.5)	146.5	139.7 7.6 (139.8) (7.8)	147.9	137.7 7.3 (137.7) (7.4)	145.7 (145.7)
C-4'	101.7 6.7	101.5 6.5	99.5 6.4	98.9 6.2	105.0 6.4 (103.1) (6.6)	104.5 6.2 (102.7) (6.4)	102.3 6.0 (101.4) (6.4)	101.6 5.8 (100.6) (6.2)	103.1 6.4 (103.6) (6.5)	102.8 6.2 (103.3) (6.3)	101.8 5.9 (101.0) (6.2)	101.0 5.7 (100.2) (6.0)
C-5'	134.5	134.8	134.7	135.0	138.4 (138.9)	138.5 (139.0)	138.5 (138.7)	138.8 (139.0)	140.0 (140.3)	140.1 (140.4)	140.2 (140.2)	140.2 (140.4)
CO	156.6	156.7	156.2	156.1	158.8 (159.6)	158.4 (159.5)	159.1 (159.5)	159.1 (159.5)	161.3 (162.6)	161.2 (162.7)	162.0 (162.0)	161.8 (162.1)
NH	11.3	11.3	11.2	11.2								

Table 1 (continued).

	3a	3b	3c	3d	4a	4b	4c	4d	6a	6b	6c	6d
NCH_3					37.9	37.8	36.2	36.2	37.5	37.4	36.3	36.4
					3.6	3.5	3.4	3.4	3.4	3.4	3.2	3.2
					(38.5)	(38.5)	(38.6)	(38.6)	(38.7)	(38.7)	(38.8)	(38.8)
					(3.2)	(3.1)	(3.2)	(3.2)	(3.0)	(3.0)	(3.2)	(3.1)
N-1-CH_2CH_3	46.1	46.2	46.4	46.4	45.1	45.1	46.2	46.3	44.8	44.2	45.1	45.1
	4.0	4.0	4.2	4.2	3.0	3.0	4.2	4.1	2.9	3.0	4.0	4.0
					(45.9)	(45.9)	(46.5)	(46.6)	(44.8)	(44.8)	(45.2)	(45.2)
					(3.7) [b]	(3.7) [b]	(4.2)	(4.2)	(3.7)	(3.8)	(4.1)	(4.1)
N-1-CH_2CH_3	15.0	15.0	14.9	15.0	14.6	14.5	14.4	14.5	15.0	14.9	15.1	15.1
	1.3	1.3	1.4	1.4	1.1	1.1	1.3	1.3	1.0	1.0	1.3	1.3
					(14.7)	(14.7)	(14.5)	(14.6)	(15.5)	(15.5)	(15.4)	(15.4)
					(1.2)	(1.2)	(1.4)	(1.4)	(1.1)	(1.1)	(1.3)	(1.3)
C-3-CH_3	13.1	13.2	13.1	13.1	12.8	12.8	12.9	13.0	11.2	11.3	11.2	11.3
	2.5	2.5	2.5	2.5	2.3	2.3	2.3	2.3	2.0	2.0	2.0	2.0
					(13.2)	(13.2)	(13.1)	(13.2)	(11.1)	(11.3)	(11.1)	(11.0)
					(2.5)	(2.5)	(2.5)	(2.5)	(2.1)	(2.1)	(2.1)	(2.1)
N*H*$COCH_3$									8.9	8.9	9.1	9.1
									(9.5)	(9.4)	(9.5)	(9.5)
NH*C*OCH_3									167.2	167.2	167.5	167.4
									(168.2)	(168.3)	(168.4)	(168.3)
NHCO*C*H_3									22.6	22.5	22.5	22.5
									1.9	1.9	2.0	2.0
									(22.4)	(22.4)	(22.5)	(22.5)
									(2.0)	(2.0)	(2.0)	(2.0)
$R_1 = CH_3$			35.7	35.4			35.4	35.1			35.2	34.8
			3.8	3.7			3.7	3.6			3.6	3.4
							(35.8)	(35.5)			(35.8)	(35.3)
							(3.8)	(3.7)			(3.7)	(3.6)
R_1 = Ph: C-1	138.2	138.4			137.4	137.3			137.9	137.9		
					(138.3)	(138.3)			(138.5)	(138.5)		
C-2,6	124.4	124.3			123.5	123.2			123.3	123.2		
	7.6	7.5			7.3	7.2			7.2	7.0		
					(124.5)	(124.2)			(123.9)	(123.6)		
					(7.6)	(7.5)			(7.5)	(7.5)		
C-3,5	129.2	129.2			129.9	129.7			129.3	129.2		
	7.5	7.5			7.6	7.5			7.5	7.4		
					(129.3)	(129.3)			(129.3)	(129.2)		
					(7.6)	(7.5)			(7.5)	(7.4)		
C-4	128.0	127.7			128.4	128.0			127.7	127.3		
	7.5	7.4			7.5	7.5			7.4	7.3		
					(128.5)	(128.1)			(128.1)	(127.7)		
					(7.5)	(7.5)			(7.4)	(7.4)		
$R_2 = CH_3$		13.7		13.5		13.6		13.4		13.8		13.6
		2.3		2.1		2.1		2.0		2.2		2.0
						(13.8)		(13.6)		(13.8)		(13.6)
						(2.3)		(2.2)		(2.3)		(2.1)

[a] Chemical shift values are given in ppm downfield from internal TMS in DMSO-d_6 solutions. The values in parentheses are for the less abundant isomer (25-45%). [b] In the proton spectra recorded at 23° two different resonances are detected for the methylene protons: **4a**, 3.6 and 3.7 ppm; **4b**, 3.6 and 3.7 ppm, respectively.

rings in the carbon-13 nmr spectra indicated that the cyclisation took place. A complete assignment of the chemical shifts to the carbon atoms of compounds **7** was once again performed by different nmr experiments, such as DEPT and XHDEPT for one-bond C-H correlations, and mainly COLOC experiments for long-range C-H correlations, which allowed us to determine the exact sequence of the carbon atoms of the central ring in the spectra. It is noteworthy that the proton spectra of compounds **4**, **6**, and **7** gave evidence of two different multiplets for the *N*-methylene protons, which resulted from magnetic non-equivalence due to hindered rotation around to the N-C bond: a little rise in temperature (93° for **4** and **6**) produced signals coalescence. Finally, experiments aimed to evidence the activity of the compounds **7** on CNS are in progress and will be reported on elsewhere.

Table 2

^{13}C-and ^{1}H-NMR Chemical Shift Values of Compounds **7** [a]

	7a	**7b**	**7c**	**7d**
C-3	140.9	140.6	140.3	139.8
C-3a	130.5	130.9	130.6	130.9
C-5	161.8	162.6	162.4	163.3
C-5a	114.4	112.9	112.8	111.0
C-6	138.0	144.8	135.7	142.3
	8.0		7.6	
C-8a	138.6	139.0	139.4	139.7
C-10	161.9	161.9	161.7	161.7
C-10a	125.1	124.9	125.2	124.9
NCH_2CH_3	45.3	45.1	45.2	45.0
	4.2 [b]	4.2 [b]	4.1 [b]	4.1 [b]
NCH_2CH_3	15.6	15.6	15.5	15.5
	1.4	1.4	1.3	1.2
C-3-CH_3	10.7	10.7	10.5	10.5
	2.1	2.0	2.0	2.0
C-5-CH_3	28.1	27.1	28.0	27.0
	2.5	2.5	2.4	2.4
R_1 = Ph: C-1	137.6	137.5		
C-2,6	123.4	123.1		
	7.4	7.4		
C-3,5	130.0	130.0		
	7.6	7.6		
C-4	128.9	128.6		
	7.5	7.5		
R_1: CH_3			36.1	35.5
			3.8	3.6
R_2: CH_3		13.4		13.0
		2.3		2.1
NCH_3	34.8	34.6	35.4	35.1
	2.8	2.7	3.3	3.2

[a] Chemical shift values are given in ppm downfield from internal TMS in DMSO-d_6 solutions. [b] In proton spectra recorded at 23° two different resonances are detected for the methylene protons: **7a**, 4.1 and 4.2 ppm; **7b**, 4.1 and 4.2 ppm; **7c**, 4.0 and 4.1 ppm; **7d**, 4.0 and 4.1 ppm, respectively.

EXPERIMENTAL

Melting points were measured in open capillary tubes, using a Buchi-Tottoli immersion apparatus, and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Infracord 137 spectrophotometer as nujol mulls. The ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AC 250 spectrometer operating in FT mode at 250.13 and 62.89 MHz, respectively, in dimethyl sulfoxide-d_6 solutions. TMS was used as an internal standard. The ^{13}C nmr chemical shifts values were measured from proton fully decoupled spectra. The assignment was supported by DEPT experiments, together with 2D C-H correlation experiments by using standard Bruker pulse sequences (XHDEPT.AUR and COLOC.AUR, for one-bond and long-range C-H interactions, respectively). Variable temperature experiments were run on a Bruker AMX 500 spectrometer, in the range 23-93°. Mass spectra (only for the compounds **7a-d**) were recorded on a JEOL JMS-01-SG-2 spectrometer at 75 eV (100 μA). Elemental analyses were determined by Labo. de Chimie Pharmaceutique - Service de microchimie - Dr. H. Eder, Université de Geneve, Suisse.

General Procedure for the Synthesis of 1-Ethyl-3-methyl-4-nitro-*N*-(1-R_1-3-R_2-1*H*-pyrazol-5-yl)-1*H*-pyrazole-5-carboxamides **3a-d**.

A solution of **1** (10 mmoles), aminopyrazoles **2a-d** (10 mmoles) and triethylamine (10 mmoles) in chloroform (50 ml) was stirred at room temperature for 24 hours. The solvent was then evaporated under reduced pressure and the residue was recrystallized from ethanol.

Compound **3a** (R_1 = C_6H_5, R_2 = H) was obtained in a yield of 73%, mp 155-156°; ir: 3150 (NH), 1690 (CO) cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}O_3N_6$: C, 56.46; H, 4.74; N, 24.70. Found: C, 56.40; H, 4.67; N, 24.58.

Compound **3b** (R_1 = C_6H_5, R_2 = CH_3) was obtained in a yield of 70%, mp 190-191°; ir: 3150 (NH), 1700 (CO) cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}O_3N_6$: C, 57.62; H, 5.12; N, 23.72. Found: C, 57.67; H, 5.10; N, 23.63.

Compound **3c** (R_1 = CH_3, R_2 = H) was obtained in a yield of 71%, mp 207-208°; ir: 3250 (NH), 1670 (CO) cm^{-1}.

Anal. Calcd. for $C_{11}H_{14}O_3N_6$: C, 47.48; H, 5.07; N, 30.20. Found: C, 47.41; H, 5.02; N, 30.21.

Compound **3d** (R_1 = CH_3, R_2 = CH_3) was obtained in a yield of 74%, mp 167-168°; ir: 3250 (NH), 1670 (CO) cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}O_3N_6$: C, 49.31; H, 5.52; N, 28.75. Found: C, 49.25; H, 5.55; N, 28.50.

General Procedure for the Preparation of 1-Ethyl-*N*,3-dimethyl-4-nitro-*N*-(1-R_1-3-R_2-1*H*-pyrazol-5-yl)-1*H*-pyrazole-5-carboxamides **4a-d**.

A solution of **3a-d** (3 mmoles) in 10% aqueous potassium hydroxide (50 ml) was treated with dimethyl sulfate (8 ml) and stirred at room temperature for 3 hours and then allowed to stand at 10° for 30 minutes. The solid precipitated was collected and recrystallized from ethanol.

Compound **4a** (R_1 = C_6H_5, R_2 = H) was obtained in a yield of 65%, mp 145-145°; ir: 1670 (CO) cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}O_3N_6$: C, 57.62; H, 5.12; N, 23.72. Found: C, 57.72; H, 5.14; N, 23.80.

Compound **4b** (R_1 = C_6H_5, R_2 = CH_3) was obtained in a yield of 68%, mp 155-156°; ir: 1680 (CO) cm^{-1}.

Anal. Calcd. for $C_{18}H_{20}O_3N_6$: C, 58.68; H, 5.47; N, 22.81. Found: C, 58.69; H, 5.47; N, 22.66.

Compound **4c** (R_1 = CH_3, R_2 = H) was obtained in a yield of 64%, mp 168-169°; ir: 1680 (CO) cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}O_3N_6$: C, 49.31; H, 5.52; N, 28.75. Found: C, 49.44; H, 5.49; N, 28.85.

Compound **4d** (R_1 = CH_3, R_2 = CH_3) was obtained in a yield of 67%, mp 130-131°; ir: 1670 (CO) cm^{-1}.

Anal. Calcd. for $C_{13}H_{18}O_3N_6$: C, 50.97; H, 5.92; N, 27.44. Found: C, 50.74, H, 5.88; N, 27.52.

Hydrolysis of **4a**.

Four mmoles of **4a** in ethanol (10 ml) were refluxed with 20% aqueous potassium hydroxide (5.0 ml) for 10 hours. Then the solution was concentrated to small volume and extracted with chloroform. The organic extract was collected, dried (magnesium sulfate) and evaporated. The solid residue, which was recrystallized from toluene, was identical in all the respects with an authentic sample of 5-methylamino-1-phenylpyrazole (mp, ir, tlc) [9].

General Procedure for the Synthesis of 1-Ethyl-*N*,3-dimethyl-4-

acetamido-*N*-(1-R_1-3-R_2-1*H*-pyrazol-5-yl)-1*H*-pyrazole-5-carboxamides **6a-d**.

A mixture of **4a-d** (4 mmoles) in ethanol (100 ml) and 1 g of W-2 Raney-Nickel was hydrogenated in a Parr apparatus at 45-50 psi for 20 hours at room temperature. Removal of the catalyst and evaporation of the solvent left the crude product which was treated with acetic anhydride (20 ml) and stirred at room temperature for 24 hours. After evaporation to dryness under reduced pressure, the residue was poured into crushed ice, mixed with solid sodium bicarbonate and extracted with chloroform (2 x 50 ml). The organic layers were washed with water, dried (magnesium sulfate) and concentrated under reduced pressure to dryness to give a residue which was recrystallized from toluene.

Compound **6a** (R_1 = C_6H_5, R_2 = H) was obtained in a yield of 72%, mp 168-169°; ir: 3220 (NH), 1680 (CO), cm^{-1}.

Anal. Calcd. for $C_{19}H_{22}O_2N_6$: C, 62.28; H, 6.05; N, 22.94. Found: C, 62.35; H, 6.25; N, 22.81.

Compound **6b** (R_1 = C_6H_5, R_2 = CH_3) was obtained in a yield of 80%, mp 180-181°; ir: 3250 (NH), 1680 (CO) cm^{-1}.

Anal. Calcd. for $C_{20}H_{24}O_2N_6$: C, 63.14; H, 6.36; N, 22.09. Found: C, 63.26; H, 6.32; N, 22.16.

Compound **6c** (R_1 = CH_3, R_2 = H) was obtained in a yield of 73%, mp 162-163°; ir: 3280 (NH), 1680 (CO) cm^{-1}.

Anal. Calcd. for $C_{14}H_{20}O_2N_6$: C, 55.25; H, 6.62; N, 27.62. Found: C, 55.29; H, 6.57; N, 27.72.

Compound **6d** (R_1 = CH_3, R_2 = CH_3) was obtained in a yield of 60%, mp 170-171°; ir: 3240 (NH), 1680 (CO) cm^{-1}.

Anal. Calcd. for $C_{15}H_{22}O_2N_6$: C, 56.59; H, 6.97; N, 26.40. Found: C, 56.48; H, 7.02; N, 26.36.

General Procedure for the Synthesis of 1-Ethyl-8,9-dihydro-3,5,9-trimethyl-6-R_2-8-R_1-dipyrazolo[3,4-*b*:4',3'-*f*][1,5]diazocin-10(1*H*)-ones **7a-d**.

A mixture of **6a-d** (2 mmoles) and phosphorus oxychloride (25 ml) was refluxed at 150-160° for 2 hours. Excess phosphorus oxychloride was evaporated under reduced pressure and the mixture was poured into crushed ice, the solution was adjusted to *p*H 8.3 with solid sodium bicarbonate and extracted with chloroform (3 x 50 ml). The organic layers were washed with water, dried (magnesium sulfate) and concentrated to dryness to give a residue wich was recrystallized from toluene.

Compound **7a** (R_1 = C_6H_5, R_2 = H) was obtained in a yield of 65%, mp 173-174°; ir: 1670 (CO) cm^{-1}; ms: m/z 348 (molecular ion).

Anal. Calcd. for $C_{19}H_{20}ON_6$: C, 65.50; H, 5.79; N, 24.12. Found: C, 65.34; H, 5.82; N, 24.06.

Compound **7b** (R_1 = C_6H_5, R_2 = CH_3) was obtained in a yield of 69%, mp 207-208°; ir: 1670 (CO) cm^{-1}; ms: m/z 362 (molecular ion).

Anal. Calcd. for $C_{20}H_{22}ON_6$: C, 66.28; H, 6.12; N, 23.19. Found: C, 66.12; H, 6.14; N, 23.10.

Compound **7c** (R_1 = CH_3, R_2 = H) was obtained in a yield of 73%, mp 190-191°; ir: 1660 (CO) cm^{-1}; ms: m/z 286 (molecular ion).

Anal. Calcd. for $C_{14}H_{18}ON_6$: C, 58.72; H, 6.34; N, 29.35. Found: C, 58.60; H, 6.32; N, 29.32.

Compound **7d** (R_1 = CH_3, R_2 = CH_3) was obtained in a yield of 75%, mp 187-188°; ir: 1670 (CO) cm^{-1}; ms: m/z 300 (molecular ion).

Anal. Calcd. for $C_{15}H_{20}ON_6$: C, 59.98; H, 6.71; N, 27.98. Found: C, 59.86; H, 6.72; N, 27.96.

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