

STUDIES ON THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS. PART XII. PYRAZOLO[4,3-c]-1,5-BENZODIAZOCINE-4,10-DIONE. A NEW RING SYSTEM

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**Abstract** — Treatment of *N*-(1-*R*-4-carboxypyrazol-5-yl)-2-aminobenzamides **2b,e** with thionyl chloride afforded new pyrazolo[3,4-d]-1,3-oxazinones **3b,e**. When the amide group of compounds **2b,e** was blocked pyrazolo[4,3-c]-1,5-benzodiazocine-4,10-diones **6a,d** were obtained.

In connection with a synthetic program of new types of pyrazole derivatives involving potential biological activities<sup>1</sup> and in order to evaluate the usefulness of the intermediates *N*-(1-*R*-4-carboxypyrazol-5-yl)-2-aminobenzamides **2b,e** for the synthesis of pyrazolo[4,3-c]-1,5-benzodiazocinones of type **6**, we decided to attempt cyclization of **2b,e** to give **6**. When compounds **2b,e** were treated with thionyl chloride, only products formulated as pyrazolo[3,4-d]-1,3-oxazinones **3b,e** were obtained.

It was discovered that compound **3b** exhibited an antiinflammatory activity. This observation prompted us to synthesize some compounds of type **3**, with the purpose of testing for analgesic, antipyretic and antiinflammatory activities.<sup>2</sup>

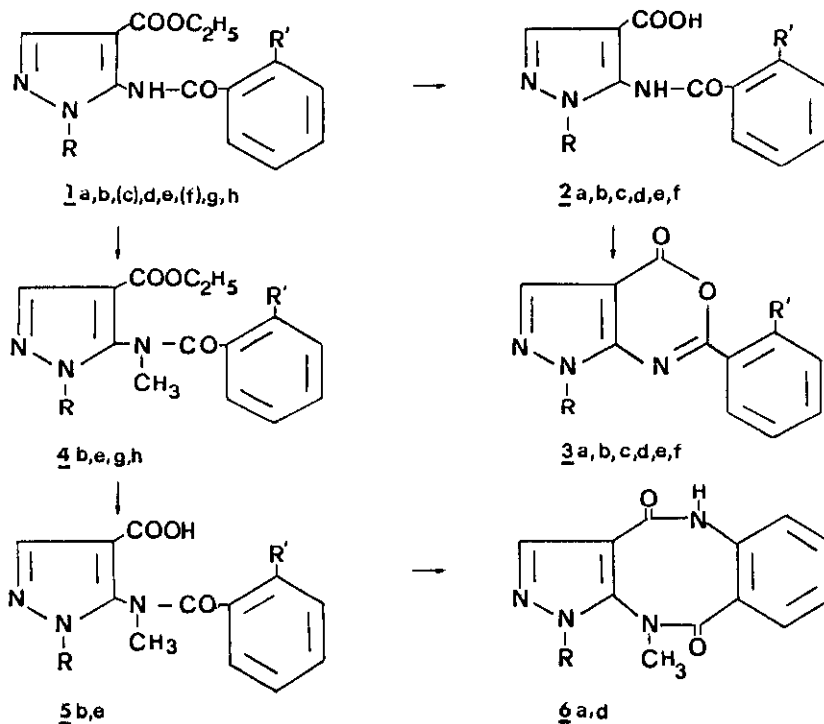
We prepared the new compounds **1a,(c),d**, as starting materials, by recently reported methods<sup>1,3</sup>. The ester moiety in **1** was readily hydrolyzed to yield the acids **2** which, in turn, when refluxed in benzene with thionyl chloride formed a new compound, which could be considered to contain the lactone structure **3** or the tricyclic form **6**. (Scheme)

The ir spectra of compounds **3** exhibit a strong band in the 1770-1810 cm<sup>-1</sup> region, which supports the lactone structure **3**.

Moreover, this structural assignment is substantiated by the nmr spectroscopic examination which shows the presence of a NH<sub>2</sub> broad signal (2H) at δ 6.26 (**3b**) and δ 6.25 (**3e**) respectively, exchangeable with deuterium oxide.

At this point of the work, it was decided to block the amide group of *N*-(1-*R*-4-carboxypyrazol-5-yl)-2-nitrobenzamides **1g,h** by methylating. Thus, treatment of **1g,h** with methyl iodide and KOH in acetone and successive reduction of obtained products **4g,h** gave *N*-methyl-(1-*R*-4-carboxypyrazol-5-yl)-2-aminobenzamides **4b,e**. The nmr spectrum of **4g** showed four sharp reso-

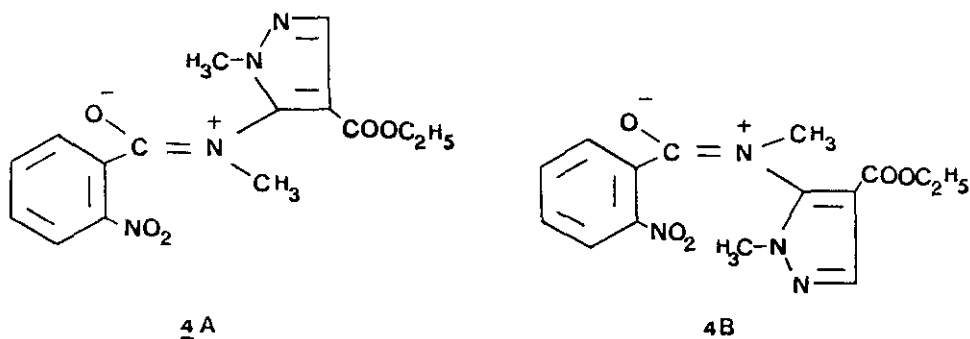
Scheme



	a	b	c	d	e	f	g	h
R	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
R'	H	NH <sub>2</sub>	OH	H	NH <sub>2</sub>	OH	NO <sub>2</sub>	NO <sub>2</sub>

nances for the magnetically non-equivalent N-methyl groups, due to the presence of different isomers 4A and 4B, as a consequence of the partial double bond character of the amide group. However, on heating to 150°C, the nmr spectrum showed two sharp singlet for each methyl group. Likewise, the nmr spectrum of 4h, at room temperature, exhibited two sharp resonance lines for N-methyl group. Basic hydrolysis of the pyrazole esters 4b,e afforded the corresponding acids 5b,e, which in turn, when refluxed in benzene with thionyl chloride formed the new pyrazoloben-zodiazocines 6a,d, whose structures were consistent with molecular weight (mass spectrum), molecular formula (analytical data) and spectral data.

In fact, their ir spectra showed carbonyl stretchings at 1640-1670 cm<sup>-1</sup> (amidic C=O) and NH



stretching vibrations at  $3200\text{--}3300\text{ cm}^{-1}$ . The nmr spectra exhibited, besides other signals for the remaining protons, a sharp singlet (1H) at  $\delta$  9.81 (6a) and  $\delta$  10.01 (6d) exchangeable with deuterium oxide, attributable to the NH resonance.

Further studies directed towards the synthesis of the new pyrazoloxazinones 3 containing pharmacological activities is the subject of a future report from these laboratories.

#### EXPERIMENTAL

Melting points were measured with a Büchi-Tottoli apparatus and are uncorrected. Proton nuclear magnetic resonance ( $^1\text{H-NMR}$ ) spectra were obtained in the indicated solvent on a Varian FT80A (80 MHz) spectrometer with TMS as an internal reference. Infrared spectra were determined in Nujol mull with a Jasco IR 810 spectrophotometer and Jeol JMS-01-SG-2 mass spectrometer was used to determine mass spectra (MS).

#### General Procedure for N-(1-R-4-Carbethoxypyrazol-5-yl)-benzamides (1a,d).

Equimolar amounts (20 mmoles) of 1-R-4-carbethoxy-5-aminopyrazole ( $\text{R}=\text{CH}_3, \text{C}_6\text{H}_5$ )<sup>4,5</sup> and benzoyl chloride (2.6 ml) in acetonitrile (50 ml) were refluxed for 7 h. Excess solvent was distilled off under reduced pressure. The solid separated was recrystallized from ethanol.

#### N-(1-Methyl-4-carbethoxypyrazol-5-yl)-benzamide (1a).

Yield 80%. Mp  $92\text{--}95^\circ\text{C}$ . Ir  $\nu$  (Nujol)  $1685\text{ cm}^{-1}$  (broad, CO),  $3380\text{ cm}^{-1}$  (NH); nmr  $\delta$  ( $\text{CDCl}_3$ ) 1.33(t, 3H,  $\text{CH}_3$ ,  $J=7\text{Hz}$ ), 3.94(s, 3H,  $\text{CH}_3$ ), 4.32(q, 2H,  $\text{CH}_2$ ,  $J=7\text{Hz}$ ), 7.30-8.20(a set of signals, 6H,  $\text{C}_6\text{H}_5$  and pyrazole H-3), 9.30(broad, 1H, NH, exchangeable); ms  $m/z$  273( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3$ : C, 61.53; H, 5.53; N, 15.38. Found: C, 61.62; H, 5.48; N, 15.44.

#### N-(1-Phenyl-4-carbethoxypyrazol-5-yl)-benzamide (1d).

Yield 80%. Mp  $97\text{--}100^\circ\text{C}$ . Ir  $\nu$  (Nujol)  $1655\text{--}1685\text{ cm}^{-1}$  (2xCO),  $3200\text{ cm}^{-1}$  (broad, NH),  $3460\text{--}3490\text{ cm}^{-1}$  (NH); nmr  $\delta$  ( $\text{CDCl}_3$ ) 1.30(t, 3H,  $\text{CH}_3$ ,  $J=7\text{Hz}$ ), 4.24(q, 2H,  $\text{CH}_2$ ,  $J=7\text{Hz}$ ), 7.30-8.15(a set of signals, 10H,  $\text{C}_6\text{H}_5$ ,  $\text{C}_6\text{H}_4$  and pyrazole H-3), 9.37(s, 1H, exchangeable, NH); ms  $m/z$  335( $\text{M}^+$ ). Anal. Calcd for

$C_{19}H_{17}N_3O_3$ : C, 68.05; H, 5.11; N, 12.53. Found: C, 67.80; H, 5.00; N, 12.70.

Hydrolysis of N-(1-R-4-Carboxypyrazol-5-yl)-2-R'-benzamides (2a,b,d,e and 5b,e).

To a solution of the esters 1a,b<sup>1</sup>,d,e<sup>1</sup> or 4b,e (see below) (1 g) in ethanol (10 ml) a solution of 4% aqueous sodium hydroxide (30 ml) was added. The mixture was refluxed for 15 min and then treated with dilute hydrochloric acid (until pH 2.5 for 1a,d and 4.5 for 1b,e). The precipitate was filtered off and recrystallized from ethanol to give pure 2a,b,d,e or 5b,e (see below).

N-(1-Methyl-4-carboxypyrazol-5-yl)-benzamide (2a).

Yield 60%. Mp 205-208°C. Ir  $\nu$  (Nujol) 1685  $cm^{-1}$  (2xCO, broad), 2500-3120  $cm^{-1}$  (OH, multiple bands), 3340  $cm^{-1}$  (NH); nmr  $\delta$  (DMSO- $d_6$ ) 3.73(s, 3H,  $CH_3$ ), 7.4-8.3(a set of signals, 6H,  $C_6H_5$  and pyrazole H-3), 10.57(very broad, exchangeable); ms m/z 245( $M^+$ ). Anal. Calcd for  $C_{12}H_{11}N_3O_3$ : C, 58.77; H, 4.52; N, 17.14. Found: C, 58.50; H, 4.56; N, 16.86.

N-(1-Methyl-4-carboxypyrazol-5-yl)-2-aminobenzamide (2b).

Yield 80%. Mp 220-221°C (methanol). Ir  $\nu$  (Nujol) 1710 and 1690  $cm^{-1}$  (2xCO), 2470-3200  $cm^{-1}$  (OH), 3360-3460  $cm^{-1}$  (multiple bands, NH and  $NH_2$ ); nmr  $\delta$  (DMSO- $d_6$ ) 3.69(s, 3H,  $CH_3$ ), 6.71-7.84 (a set of signals, 5H,  $C_6H_4$ , pyrazole H-3); ms m/z 260( $M^+$ ). Anal. Calcd for  $C_{12}H_{12}N_4O_3$ : C, 55.38; H, 4.65; N, 21.53. Found: C, 55.25; H, 4.50; N, 21.73.

N-(1-Phenyl-4-carboxypyrazol-5-yl)-benzamide (2d).

Yield 60%. Mp 212-215°C. Ir  $\nu$  (Nujol) 1650-1683  $cm^{-1}$  (2xCO), 2500-3200  $cm^{-1}$  (OH), 3280  $cm^{-1}$  (broad, NH); nmr  $\delta$  (DMSO- $d_6$ ) 7.30-8.30(a set of signals, 11H,  $C_6H_5$ ,  $C_6H_4$  and pyrazole H-3); ms m/z 307( $M^+$ ). Anal. Calcd for  $C_{17}H_{13}N_3O_3$ : C, 66.44; H, 4.26; N, 13.68. Found: C, 66.58; H, 4.39; N, 13.39.

N-(1-Phenyl-4-carboxypyrazol-5-yl)-2-aminobenzamide (2e).

Yield 70%. Mp 202-204°C (methanol). Ir  $\nu$  (Nujol) 1670 and 1700  $cm^{-1}$  (2xCO), 2500-3400  $cm^{-1}$  (multiple bands, OH, NH,  $NH_2$ ); nmr  $\delta$  (DMSO- $d_6$ ) 6.59-8.19(a set of signals,  $C_6H_4$ ,  $C_6H_5$ , pyrazole H-3); ms m/z 322( $M^+$ ). Anal. Calcd for  $C_{17}H_{14}N_4O_3$ : C, 63.35; H, 4.38; N, 17.38. Found: C, 63.49; H, 4.50; N, 17.58.

N-Methyl-(1-methyl-4-carboxypyrazol-5-yl)-2-aminobenzamide (5b).

Yield 70%. Mp 176-177°C. Ir  $\nu$  (Nujol) 2500-3200  $cm^{-1}$  (OH), 3350 and 3440  $cm^{-1}$  ( $NH_2$ ); nmr  $\delta$  (DMSO- $d_6$ ) 3.19(s, 3H,  $CH_3$ ), 3.58(s, 3H,  $CH_3$ ), 6.23-7.69(a set of signals,  $C_6H_4$ , pyrazole H-3 and exchangeable protons); ms m/z 274( $M^+$ ). Anal. Calcd for  $C_{13}H_{14}N_4O_3$ : C, 56.93; H, 5.15; N, 20.43. Found: C, 56.44; H, 5.35; N, 20.00.

N-Methyl-(1-phenyl-4-carboxypyrazol-5-yl)-2-aminobenzamide (5e).

Yield 50%. Mp 115-118°C. Ir  $\nu$  (Nujol) 1645  $cm^{-1}$  and 1675-1690  $cm^{-1}$  (2xCO), 3380-3480  $cm^{-1}$  ( $NH_2$ ); nmr  $\delta$  (DMSO- $d_6$ ) 2.85(broad singlet,  $CH_3$ ), 3.36(broad singlet,  $CH_3$ ), 6.52-8.25(a set of signals, 13H,  $C_6H_5$ ,  $C_6H_4$ , pyrazole H-3 and three exchangeable protons); ms m/z 336( $M^+$ ). Anal. Calcd for  $C_{18}H_{16}N_4O_3$ : C, 64.27; H, 4.80; N, 16.66. Found: C, 64.45; H, 4.76; N, 16.57.

General Procedure for N-(1-R-4-Carboxypyrazol-5-yl)-2-hydroxybenzamides (2c,f).

1-R-4-Carbethoxy-5-aminopyrazole (60 mmoles) and phenyl salicylate (72 mmoles) were reacted

for 8 h in an oil bath at 210-215°C. The mixture, after cooling, was boiled with 100 ml of petroleum ether (bp 40-70°C) for 10 min, the solution was decanted and the insoluble material treated with petroleum ether as above. The residue obtained was suspended in 200 ml of aqueous 1N potassium hydroxide. After stirring for 45 min, the suspension was filtered off and the filtrate was allowed to stand at room temperature for 24 h. The solution was treated with concentrated hydrochloric acid until pH 3 in the ice-bath. The solid product separated was filtered off, washed with water and air dried. The crude product was dissolved in ethanol and the solution concentrated at one half volume. On standing in refrigerator overnight a crystalline product was separated (yield 30-40%).

N-(1-Methyl-4-carboxypyrazol-5-yl)-2-hydroxybenzamide (2c).

The purification for analysis of 2c requested, before the crystallization from ethanol, a column flash-chromatographic procedure (120 g of silica gel, granulometry 0.032-0.060 mm, column diameter and length 5 cm and 70 cm respectively) using ethyl acetate as eluent. The combined fractions 6-40 (each 50 ml) were evaporated to give the crude product 2c.

Yield 30%. Mp 219-221°C dec. Ir  $\nu$  (Nujol) 1655  $\text{cm}^{-1}$  and 1695  $\text{cm}^{-1}$  (2xCO), 2500-3200  $\text{cm}^{-1}$  (broad bands, COOH), 3340  $\text{cm}^{-1}$  (broad, phenolic OH and/or NH); nmr  $\delta$  (DMSO- $d_6$ ) 3.72(s, 3H,  $\text{CH}_3$ ), 6.9-8.2(a set of signals, 5H,  $\text{C}_6\text{H}_4$  and pyrazole H-3); ms  $m/z$  261( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_4$ : C, 55.17; H, 4.24; N, 16.09. Found: C, 55.11; H, 4.25; N, 15.92.

N-(1-Phenyl-4-carboxypyrazol-5-yl)-2-hydroxybenzamide (2f).

Yield 40%. Mp 230-233°C decomp. Ir  $\nu$  (Nujol) 1650 and 1685  $\text{cm}^{-1}$  (2xCO), 2600-3300  $\text{cm}^{-1}$  (NH, OH); nmr  $\delta$  (DMSO- $d_6$ ) 6.92-8.24(a set of signals, 10H,  $\text{C}_6\text{H}_4$ ,  $\text{C}_6\text{H}_5$  and pyrazole H-3), 10.70(broad, 1H, exchangeable), 11.63(broad, 1H, exchangeable), 12.50(broad, 1H, exchangeable); ms  $m/z$  323( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_4$ : C, 63.15; H, 4.05; N, 13.00. Found: C, 63.20; H, 4.04; N, 12.92.

General Procedure for Pyrazolo[3,4-d]-1,3-oxazin-4(1H)-ones (3) or Pyrazolo[4,3-c]-1,5-benzodiazocine-4,10-diones (6).

Thionyl chloride (10 ml) was added to a suspension of 2 or 5 (30 mmoles) in anhydrous benzene (55 ml). The mixture was refluxed for 4 h, then cooled and the solid precipitate was filtered off and recrystallized from ethanol (compounds 3c,f from benzene).

1-Methyl-6-phenylpyrazolo[3,4-d]-1,3-oxazin-4(1H)-one (3a).

Yield 50%. Mp 155-158°C. Ir  $\nu$  (Nujol) 1770  $\text{cm}^{-1}$  (broad, CO); nmr  $\delta$  ( $\text{CDCl}_3$ ) 4.01(s, 3H,  $\text{CH}_3$ ), 7.32-8.43(a set of signals, 6H,  $\text{C}_6\text{H}_5$  and pyrazole H-3); ms  $m/z$  227( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{12}\text{H}_9\text{N}_3\text{O}_2$ : C, 63.43; H, 3.99; N, 18.49. Found: C, 63.24; H, 4.01; N, 18.78.

1-Methyl-6-o-aminophenylpyrazolo[3,4-d]-1,3-oxazin-4(1H)-one (3b).

Yield 80%. Mp 210°C. Ir  $\nu$  (Nujol) 1780  $\text{cm}^{-1}$  (CO), 3500-3350  $\text{cm}^{-1}$  (multiple bands,  $\text{NH}_2$ ); nmr  $\delta$  ( $\text{CDCl}_3$ ) 4.03(s, 3H,  $\text{CH}_3$ ), 6.26(broad,  $\text{NH}_2$  exchangeable), 6.70-8.24(a set of signals, 5H,  $\text{C}_6\text{H}_4$  and pyrazole H-3); ms  $m/z$  242( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_2$ : C, 59.50; H, 4.16; N, 23.13. Found: C, 59.60; H, 4.20; N, 23.20.

1-Methyl-6-o-hydroxyphenylpyrazolo[3,4-d]-1,3-oxazin-4(1H)-one (3c).

Yield 60%. Mp 222-225°C (benzene). Ir  $\nu$  (Nujol) 1785  $\text{cm}^{-1}$  (broad, CO); nmr  $\delta$  (DMSO- $d_6$ ) 4.00 (s, 3H,  $\text{CH}_3$ ), 6.80-8.40(a set of signals, 5H,  $\text{C}_6\text{H}_4$  and pyrazole H-3), 11.50(broad, OH, exchangeable); ms m/z 243( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{12}\text{H}_9\text{N}_3\text{O}_3$ : C, 59.26; H, 3.73; N, 17.28. Found: C, 59.33; H, 3.71; N, 17.09.

1,6-Diphenylpyrazolo[3,4-d]-1,3-oxazin-4(1H)-one (3d).

Yield 50%. Mp 168-169°C. Ir  $\nu$  (Nujol) 1785  $\text{cm}^{-1}$  (broad, CO); nmr  $\delta$  ( $\text{CDCl}_3$ ) 7.30-8.43(a set of signals,  $2\times\text{C}_6\text{H}_5$  and pyrazole H-3); ms m/z 289( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{17}\text{H}_{11}\text{N}_3\text{O}_2$ : C, 70.58; H, 3.83; N, 14.53. Found: C, 70.45; H, 3.82; N, 14.44.

1-Phenyl-6-o-aminophenylpyrazolo[3,4-d]1,3-oxazin-4(1H)-one (3e).

Yield 80%. Mp 170-172°C. Ir  $\nu$  (Nujol) 1780 and 1805  $\text{cm}^{-1}$  (CO), 3470-3320  $\text{cm}^{-1}$  (multiple bands,  $\text{NH}_2$ ); nmr  $\delta$  ( $\text{CDCl}_3$ ) 6.25(broad,  $\text{NH}_2$ , exchangeable), 6.70-8.50(a set of signals, 10H,  $\text{C}_6\text{H}_4$ ,  $\text{C}_6\text{H}_5$  and pyrazole H-3); ms m/z 304( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2$ : C, 67.09; H, 3.98; N, 18.41. Found: C, 67.32; H, 4.28; N, 18.21.

1-Phenyl-6-o-hydroxyphenylpyrazolo[3,4-d]-1,3-oxazin-4(1H)-one (3f).

This compound was purified by a flash chromatographic procedure (120 g of silica gel, granulometry 0.032-0.060 mm, column diameter and length 5 cm and 70 cm respectively) using chloroform as eluent. The combined fractions 14-48 (each 50 ml) were evaporated to give the crude product 3f which was recrystallized from benzene.

Yield 70%. Mp 219-221°C. Ir  $\nu$  (Nujol) 1810  $\text{cm}^{-1}$  (very broad, CO); nmr  $\delta$  (DMSO- $d_6$ ) 6.95-8.55 (a set of signals, 10H,  $\text{C}_6\text{H}_4$ ,  $\text{C}_6\text{H}_5$  and pyrazole H-3), 11.39(s, 1H, OH); ms m/z 305( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{17}\text{H}_{11}\text{N}_3\text{O}_3$ : C, 66.88; H, 3.63; N, 13.77. Found: C, 66.84; H, 3.62; N, 13.67.

1-Methylpyrazolo[4,3-c]-1,5-benzodiazocine-4,10-dione (6a).

Yield 60%. Mp 279-280°C. Ir  $\nu$  (Nujol) 1640-1670  $\text{cm}^{-1}$  ( $2\times\text{CO}$ ), 3300  $\text{cm}^{-1}$  (NH); nmr  $\delta$  (DMSO- $d_6$ ) 3.28(s, 3H,  $\text{CH}_3$ ), 3.71(s, 3H,  $\text{CH}_3$ ), 7.11-7.52(a set of signals, 5H,  $\text{C}_6\text{H}_4$  and pyrazole H-3), 9.81(s, 1H, NH, exchangeable); ms m/z 256( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_2$ : C, 60.93; H, 4.72; N, 21.87. Found: C, 60.90; H, 4.80; N, 21.68.

1-Phenylpyrazolo[4,3-c]-1,5-benzodiazocine-4,10-dione (6d).

Yield 30%. Mp 248-249°C. Ir  $\nu$  (Nujol) 1650-1680  $\text{cm}^{-1}$  ( $2\times\text{CO}$ ), 3180  $\text{cm}^{-1}$  (broad, NH); nmr  $\delta$  (DMSO- $d_6$ ) 2.84(s, 3H,  $\text{CH}_3$ ), 7.35-7.83(a set of signals, 10H,  $\text{C}_6\text{H}_4$ ,  $\text{C}_6\text{H}_5$  and pyrazole H-3), 10.01(s, 1H, NH, exchangeable); ms m/z 318( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_2$ : C, 67.91; H, 4.43; N, 17.60. Found: C, 67.67; H, 4.56; N, 17.33.

General Procedure for N-Methyl-(1-R-4-carbethoxy-pyrazol-5-yl)-2-nitrobenzamide (4g,h).

To a solution of 1g,h (9.4 mmoles) in hot acetone (33 ml) was added powdered potassium hydroxide (1.87 g), followed by addition of methyl iodide (0.87 ml) in acetone (5 ml). The mixture was refluxed for 30 min. It was then filtered and the resulting solution was concentrated. The addition of water and cooling resulted in the precipitation of the crude product 4g,h which was recrystallized from ethanol.

N-Methyl-(1-methyl-4-carbethoxy-pyrazol-5-yl)-2-nitrobenzamide (4g).

Yield 90-95%. Mp 115-116°C. Ir  $\nu$  (Nujol) 1680-1710  $\text{cm}^{-1}$  (2xCO); nmr  $\delta$  (DMSO- $d_6$  at 75°C) 1.37(s, 3H,  $\text{CH}_3$ , J=6Hz), 3.15(s,  $\text{CH}_3$ ), 3.4(s,  $\text{CH}_3$ ), 3.65(s,  $\text{CH}_3$ ), 3.96(s,  $\text{CH}_3$ ), 4.00-4.33(superimposed quadruplets, 2H,  $\text{CH}_2$ ), 7.00-8.40(a set of signals, 5H,  $\text{C}_6\text{H}_4$  and pyrazole H-3); nmr  $\delta$  (DMSO- $d_6$  at 150°C) 1.36(t, 3H,  $\text{CH}_3$ , J=7Hz), 3.27(s, 3H,  $\text{CH}_3$ ), 3.80(s, 3H,  $\text{CH}_3$ ), 4.35(q, 2H,  $\text{CH}_2$ , J=7Hz); ms m/z 302( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_5$ : C, 54.21; H, 4.85; N, 16.86. Found: C, 54.47; H, 4.90; N, 16.80.

N-Methyl-(1-phenyl-4-carbethoxy-pyrazol-5-yl)-2-nitrobenzamide (4h).

Yield 90-95%. Mp 126-127°C. Ir  $\nu$  (Nujol) 1670 and 1710  $\text{cm}^{-1}$  (2xCO); nmr  $\delta$  (DMSO- $d_6$ ) 1.32(m, 3H,  $\text{CH}_3$ ), 3.01(s,  $\text{CH}_3$ ), 3.02(s,  $\text{CH}_3$ ), 3.53(s,  $\text{CH}_3$ ), 3.54(s,  $\text{CH}_3$ ), 4.34(q, 2H,  $\text{CH}_2$ , J=6.5Hz), 7.46-8.20(a set of signals, 10H,  $\text{C}_6\text{H}_4$ ,  $\text{C}_6\text{H}_5$  and pyrazole H-3); ms m/z 394( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_5$ : C, 60.91; H, 4.60; N, 14.21. Found: C, 60.84; H, 4.70; N, 14.29.

General Procedure for 2-Amino-substituted Benzamides (4b,e).

Compounds 4g,h (34 mmoles) were added to a magnetically stirred suspension of finely powdered stannous chloride (10.4 mmoles) in concentrated hydrochloric acid (5 ml) at such a rate so that the temperature of the slurry was maintained below 10°C. After the complete addition of the nitro compound, the mixture was left on a magnetic stirrer for 24 h. The white slurry thus obtained was diluted with cold water and potassium hydroxide (40%) was added. The solution was extracted with ethyl acetate (2x100 ml), the extracts were dried (sodium sulfate) and evaporated under reduced pressure to give 4b and e, which was recrystallized from ethanol.

N-Methyl-(1-methyl-4-carbethoxy-pyrazol-5-yl)-2-aminobenzamide (4b).

Yield 80%. Mp 109-112°C. Ir  $\nu$  (Nujol) 1655 and 1705  $\text{cm}^{-1}$  (2xCO), 3340 and 3450  $\text{cm}^{-1}$  ( $\text{NH}_2$ ); nmr  $\delta$  ( $\text{CDCl}_3$ ) 1.33(t, 3H,  $\text{CH}_3$ , J=7Hz), 3.34(s, 3H,  $\text{CH}_3$ ), 3.57(s, 3H,  $\text{CH}_3$ ), 4.35(q, 2H,  $\text{CH}_2$ , J=7Hz), 4.79(s, broad, 2H,  $\text{NH}_2$ , exchangeable), 6.65-7.79(a set of signals, 5H,  $\text{C}_6\text{H}_4$  and pyrazole H-3); ms m/z 302( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_3$ : C, 59.59; H, 6.00; N, 18.53. Found: C, 59.72; H, 6.05; N, 18.57.

N-Methyl-(1-phenyl-4-carbethoxy-pyrazol-5-yl)-2-aminobenzamide (4e).

Yield 50%. Mp 131-133°C. Ir  $\nu$  (Nujol) 1650 and 1700  $\text{cm}^{-1}$  (2xCO), 3380 and 3480  $\text{cm}^{-1}$  ( $\text{NH}_2$ ); nmr  $\delta$  (DMSO- $d_6$ ) 1.29(t, 3H,  $\text{CH}_3$ , J=7Hz), 3.31(3H,  $\text{CH}_3$ ), 4.29(q, 2H,  $\text{CH}_2$ , J=7Hz), 5.17(s, 2H,  $\text{NH}_2$ , exchangeable), 6.50-8.08(a set of signals, 10H,  $\text{C}_6\text{H}_4$ ,  $\text{C}_6\text{H}_5$  and pyrazole H-3); ms m/z 364( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_3$ : C, 65.92; H, 5.53; N, 15.38. Found: C, 65.83; H, 5.59; N, 15.30.

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