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[1] 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.[2]

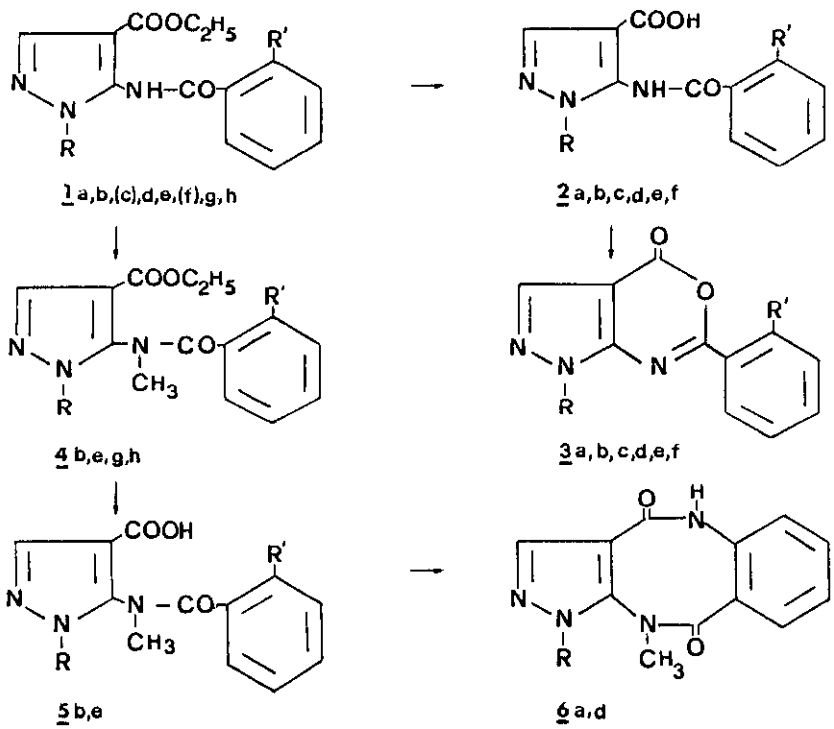
We prepared the new compounds 1a,(c),d, as starting materials, by recently reported methods[1,3]. The ester moiety in 1 was readily hydrolized to yield the acids 2 which, in turn, when refluxed in benzene with thionyl chloride formed a new compound, which could be considered to contain the lactone structure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

The ir spectra of compounds 3 exhibit a strong band in the 1770-1810 cm^{-1} 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_2 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-carbethoxypyrazol-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-carbethoxypyrazol-5-yl)-2-aminobenzamides 4b,e. The nmr spectrum of 4g showed four sharp reso-

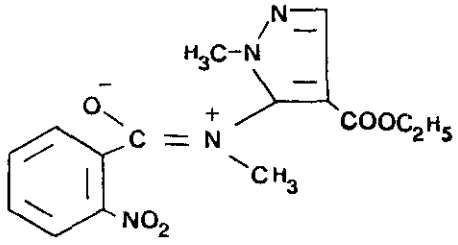
Scheme



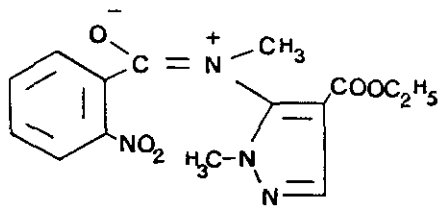
	a	b	c	d	e	f	g	h
R	CH_3	CH_3	CH_3	C_6H_5	C_6H_5	C_6H_5	CH_3	C_6H_5
R'	H	NH_2	OH	H	NH_2	OH	NO_2	NO_2

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 pyrazolobenzodiazocines 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^{-1} (amidic C=O) and NH



4A



4B

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

Furthur 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}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 (R=CH_3,C_6H_5)[4,5] 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 92-95°C. Ir ν (Nujol) 1685 cm^{-1} (broad, CO), 3380 cm^{-1} (NH); nmr δ ($CDCl_3$) 1.33(t, 3H, CH_3, J≈7Hz), 3.94(s, 3H, CH_3), 4.32(q, 2H, CH_3, J≈7Hz), 7.30-8.20(a set of signals, 6H, C_6H_5 and pyrazole H-3), 9.30(broad, 1H, NH, exchangeable); ms m/z 273(M^+). Anal. Calcd for $C_{14}H_{15}N_3O_3$: 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 97-100°C. Ir ν (Nujol) 1655-1685 cm^{-1} (2xCO), 3200 cm^{-1} (broad, NH), 3460-3490 cm^{-1} (NH); nmr δ ($CDCl_3$) 1.30(t, 3H, CH_3, J≈7Hz), 4.24(q, 2H, CH_2, J≈7Hz), 7.30-8.15(a set of signals, 10H, C_6H_5, C_6H_4 and pyrazole H-3), 9.37(s, 1H, exchangeable, NH); ms m/z 335(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[1],d,e[1] 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 ν (Nujol) 1685 cm^{-1} (2xCO, broad), 2500-3120 cm^{-1} (OH, multiple bands), 3340 cm^{-1} (NH); nmr δ (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 ν (Nujol) 1710 and 1690 cm^{-1} (2xCO), 2470-3200 cm^{-1} (OH), 3360-3460 cm^{-1} (multiple bands, NH and NH_2); nmr δ (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 ν (Nujol) 1650-1683 cm^{-1} (2xCO), 2500-3200 cm^{-1} (OH), 3280 cm^{-1} (broad, NH); nmr δ (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 ν (Nujol) 1670 and 1700 cm^{-1} (2xCO), 2500-3400 cm^{-1} (multiple bands, OH, NH, NH_2); nmr δ (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 ν (Nujol) 2500-3200 cm^{-1} (OH), 3350 and 3440 cm^{-1} (NH_2); nmr δ (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 ν (Nujol) 1645 cm^{-1} and 1675-1690 cm^{-1} (2xCO), 3380-3480 cm^{-1}(NH_2); nmr δ (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 salicilate (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 lenght 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 ν (Nujol) 1655 cm^{-1} and 1695 cm^{-1} (2xCO), 2500-3200 cm^{-1} (broad bands, COOH), 3340 cm^{-1} (broad, phenolic OH and/or NH); nmr δ (DMSO-d_6) 3.72(s, 3H, CH_3), 6.9-8.2(a set of signals, 5H, C_6H_4 and pyrazole H-3); ms m/z 261(M^+). Anal. Calcd for $C_{12}H_{11}N_3O_4$: 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 ν (Nujol) 1650 and 1685 cm^{-1} (2xCO), 2600-3300 cm^{-1} (NH, OH); nmr δ (DMSO-d_6) 6.92-8.24(a set of signals, 10H, C_6H_4, C_6H_5 and pyrazole H-3), 10.70(broad, 1H, exchangeable), 11.63(broad, 1H, exchangeable), 12.50(broad, 1H, exchangeable); ms m/z 323(M^+). Anal. Calcd for $C_{17}H_{13}N_3O_4$: 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 ν (Nujol) 1770 cm^{-1} (broad, CO); nmr δ ($CDCl_3$) 4.01(s, 3H, CH_3), 7.32-8.43(a set of signals, 6H, C_6H_5 and pyrazole H-3); ms m/z 227(M^+). Anal. Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.24; H, 4.01; N, 18.28.

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

Yield 80%. Mp 210°C. Ir ν (Nujol) 1780 cm^{-1} (CO), 3500-3350 cm^{-1} (multiple bands, NH_2); nmr δ ($CDCl_3$) 4.03(s, 3H, CH_3), 6.26(broad, NH_2 exchangeable), 6.70-8.24(a set of signals, 5H, C_6H_4 and pyrazole H-3); ms m/z 242(M^+). Anal. Calcd for $C_{12}H_{10}N_4O_2$: 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 ν (Nujol) 1785 cm^{-1} (broad, CO); nmr δ (DMSO-d_6) 4.00 (s, 3H, CH_3), 6.80-8.40(a set of signals, 5H, C_6H_4 and pyrazole H-3), 11.50(broad, OH, exchangeable); ms m/z 243(M^+). Anal. Calcd for $C_{12}H_9N_3O_3$: 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 ν (Nujol) 1785 cm^{-1} (broad, CO); nmr δ ($CDCl_3$) 7.30-8.43(a set of signals, 2xC_6H_5 and pyrazole H-3); ms m/z 289(M^+). Anal. Calcd for $C_{17}H_{11}N_3O_2$: 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 ν (Nujol) 1780 and 1805 cm^{-1} (CO), 3470-3320 cm^{-1} (multiple bands, NH_2); nmr δ ($CDCl_3$) 6.25(broad, NH_2, exchangeable), 6.70-8.50(a set of signals, 10H, C_6H_4, C_6H_5 and pyrazole H-3); ms m/z 304(M^+). Anal. Calcd for $C_{17}H_{12}N_4O_2$: 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 lenght 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 wich was recrystallized from benzene.

Yield 70%. Mp 219-221°C. Ir ν (Nujol) 1810 cm^{-1} (very broad, CO); nmr δ (DMSO-d_6) 6.95-8.55 (a set of signals, 10H, C_6H_4, C_6H_5 and pyrazole H-3), 11.39(s, 1H, OH); ms m/z 305(M^+). Anal. Calcd for $C_{17}H_{11}N_3O_3$: 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 ν (Nujol) 1640-1670 cm^{-1} (2xCO), 3300 cm^{-1} (NH); nmr δ (DMSO-d_6) 3.28(s, 3H, CH_3), 3.71(s, 3H, CH_3), 7.11-7.52(a set of signals, 5H, C_6H_4 and pyrazole H-3), 9.81(s, 1H, NH, exchangeable); ms m/z 256(M^+). Anal. Calcd for $C_{13}H_{12}N_4O_2$: 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 ν (Nujol) 1650-1680 cm^{-1} (2xCO), 3180 cm^{-1} (broad, NH); nmr δ (DMSO-d_6) 2.84(s, 3H, CH_3), 7.35-7.83(a set of signals, 10H, C_6H_4, C_6H_5 and pyrazole H-3), 10.01(s, 1H, NH, exchangeable); ms m/z 318(M^+). Anal. Calcd for $C_{18}H_{14}N_4O_2$: 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-carbethoxypyrazol-5-yl)-2-nitrobenzamide (4g,h).

To a solution of 1g,h[1] (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 resulted 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-carbethoxypyrazol-5-yl)-2-nitrobenzamide (4g).

Yield 90-95%. Mp 115-116°C. Ir ν (Nujol) 1680-1710 cm^{-1} (2xCO); nmr δ (DMSO-d_6 at 75°C) 1.37(superimposed triplets, 3H, CH_3, J≈6Hz), 3.15(s, CH_3), 3.4(s, CH_3), 3.65(s, CH_3), 3.96(s, CH_3), 4.00-4.33(superimposed quadruplets, 2H, CH_2), 7.00-8.40(a set of signals, 5H, C_6H_4 and pyrazole H-3); nmr δ (DMSO-d_6 at 150°C) 1.36(t, 3H, CH_3, J≈7Hz), 3.27(s, 3H, CH_3), 3.80(s, 3H, CH_3), 4.35 (q, 2H, CH_2, J≈7Hz); ms m/z 302(M^+). Anal. Calcd for $C_{15}H_{16}N_4O_5$: C, 54.21; H, 4.85; N, 16.86. Found: C, 54.47; H, 4.90; N, 16.80.

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

Yield 90-95%. Mp 126-127°C. Ir ν (Nujol) 1670 and 1710 cm^{-1} (2xCO); nmr δ (DMSO-d_6) 1.32(m, 3H, CH_3), 3.01(s, CH_3), 3.02(s, CH_3), 3.53(s, CH_3), 3.54(s, CH_3), 4.34(q, 2H, CH_2, J≈6.5Hz), 7.46-8.20(a set of signals, 10H, C_6H_4, C_6H_5 and pyrazole H-3); ms m/z 394(M^+). Anal. Calcd for $C_{20}H_{18}N_4O_5$: 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-carbethoxypyrazol-5-yl)-2-aminobenzamide (4b).

Yield 80%. Mp 109-112°C. Ir ν (Nujol) 1655 and 1705 cm^{-1} (2xCO), 3340 and 3450 cm^{-1} (NH_2); nmr δ ($CDCl_3$) 1.33(t, 3H, CH_3, J≈7Hz), 3.34(s, 3H, CH_3), 3.57(s, 3H, CH_3), 4.35(q, 2H, CH_2, J≈7Hz), 4.79(s, broad, 2H, NH_2, exchangeable), 6.65-7.79(a set of signals, 5H, C_6H_4 and pyrazole H-3); ms m/z 302(M^+). Anal. Calcd for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.72; H, 6.05; N, 18.57.

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

Yield 50%. Mp 131-133°C. Ir ν (Nujol) 1650 and 1700 cm^{-1} (2xCO), 3380 and 3480 cm^{-1} (NH_2); nmr δ (DMSO-d_6) 1.29(t, 3H, CH_3, J≈7Hz), 3.31(3H, CH_3), 4.29(q, 2H, CH_2, J≈7Hz), 5.17(s, 2H, NH_2, exchangeable), 6.50-8.08(a set of signals, 10H, C_6H_4, C_6H_5 and pyrazole H-3); ms m/z 364(M^+). Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38. Found: C, 65.83; H, 5.59; N, 15.30.

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