HETEROCYCLES, Vol. 75, No. 8, 2008, pp. 2035 - 2042. © The Japan Institute of Heterocyclic Chemistry
Received, 21st February, 2008, Accepted, 21st March, 2008, Published online, 28th March, 2008. COM-08-11371

2-PYRAZOLIN-5-ONES BEARING A BASIC DIALKYLAMINOALKYL SUBSTITUENT AT THE *N*1-POSITION: PREPARATION AND NMR SPECTROSCOPIC INVESTIGATIONS

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Abstract – 2-Pyrazolin-5-ones (= tautomers to 5-hydroxypyrazols) bearing dialkylaminoyalkyl substituents at the ring nitrogen atom N-1 are prepared from the corresponding hydrazines and beta-ketoesters. Detailed NMR spectroscopic investigations (^{1}H, ^{13}C, ^{15}N) with the obtained compounds are undertaken and the tautomerism of such pyrazolones in solution is discussed.

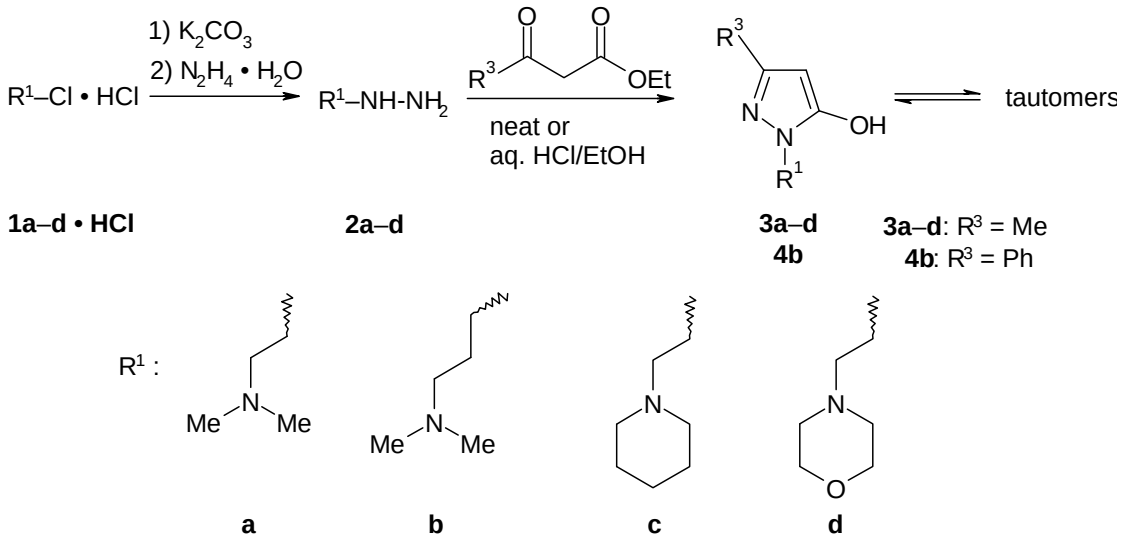
INTRODUCTION

Pyrazolones (2-pyrazolin-5-ones, systematic name: 2,4-dihydro-3*H*-pyrazol-3-ones) are valuable synthons in the construction of various pyrazole-based molecules including, amongst others, metal extracting agents, dyestuffs, photographic developers, and agrochemicals.[1–3] Furthermore, pyrazolones and derivatives thereof form the core of many biologically active compounds, comprising also many common drug molecules.[1–3] As examples phenazone, propyphenazone, and metamizole – belonging to the class of non-steroidal anti-inflammatory drugs (NSAIDs) – may serve.[4] Moreover, from a view on the space of drug molecules and biologically active compounds it emerges that basic trialkylamino groups are very frequently occurring and can be considered as one of the most important pharmacophores.[5,6] Taking these facts into account, 2-pyrazolin-5-ones carrying aminoalkyl groups at N-1 would be of great interest as building blocks for the synthesis of potentially bioactive compounds, for instance in the assembling of polycyclic heteroaromatic systems.[7–14] In continuation of our investigations on the synthetic potential and the tautomerism of pyrazolones,[7–17] we here describe the synthesis of various 2-pyrazolin-5-ones **3** and **4** with a (dimethylamino)ethyl (**a**), (dimethylamino)propyl (**b**), 2-piperidin-1-ylethyl (**c**), and 2-morpholin-4-ylmethyl (**d**) chain attached to the pyrazole N-1 (Scheme 1).

RESULTS AND DISCUSSION

Synthesis

The synthesis of the target pyrazolones (**3a**–**d**) and (**4b**) is indicated in Scheme 1. The required monosubstituted hydrazines (**2a**–**d**) were prepared by reaction of hydrazine monohydrate with the suitable alkyl halides (**1a**–**d**), the latter resulting from treatment of commercially available hydrochlorides (**1a**–**d • HCl**) with potassium carbonate. Reaction of **2a**–**d** with ethyl acetoacetate or that of **2b** with ethyl benzoylacetate was carried out in two different ways: Whereas condensation of the neat reaction partners (equimolar amounts) only in the case of **3c** led to satisfying yields, reaction in EtOH / 2N HCl afforded the pyrazolones (**3a**–**d**) and (**4b**) in high yields. With **3c** both methods gave the same results regarding yield and purity.



Scheme 1. Synthesis of the title compounds

NMR Spectroscopic Investigations

NMR spectroscopic analyses (^{1}H, ^{13}C, ^{15}N) with all prepared compounds were performed. In nearly all cases, full and unambiguous assignment for all proton, carbon, and nitrogen resonances could be achieved by combined application of standard NMR spectral techniques.[18] The ^{15}N-NMR spectra were mainly recorded using the gradient selected, sensitivity enhanced HMBC sequence.[19]

Pyrazolones (**3a**–**d**) and (**4b**) are capable of prototropic tautomerism and can exist in three tautomeric forms, namely as CH- (**A**), OH- (**B**), or NH-isomer (**C**), as indicated with **3d** (Figure 1).[1,20] The NMR spectra of these compounds are characterized by broad or even extremely broad lines, in most cases prohibiting the extraction of more detailed data, for instance the analysis of ^{13}C, ^{1}H-NMR spin coupling constants or – in case of **3a** and **3b** – ^{15}N NMR chemical shifts. This hints to the simultaneous presence of

several tautomeric forms in more or less fast exchange (compared to the NMR timescale). With compound (**3d**) in $CDCl_3$ solution the presence of individual tautomeric forms [CH-form (A) on the one hand, OH (B)/NH (C) on the other hand, ratio ~ 1.4:1] was observed, indicating slower conversion rates in this case. In contrast, in DMSO-d_6 solution the presence of an individual CH-isomer could not be detected, here the tautomeric composition is obviously dominated by the OH-isomer (B) of **3d**. The latter follows from the ^{15}N-NMR chemical shift of N-2 (δ –118.3 ppm), dominance of the NH-form is expected to lead to an explicitly smaller chemical shift for this N-atom, which then should resemble that of N-1.

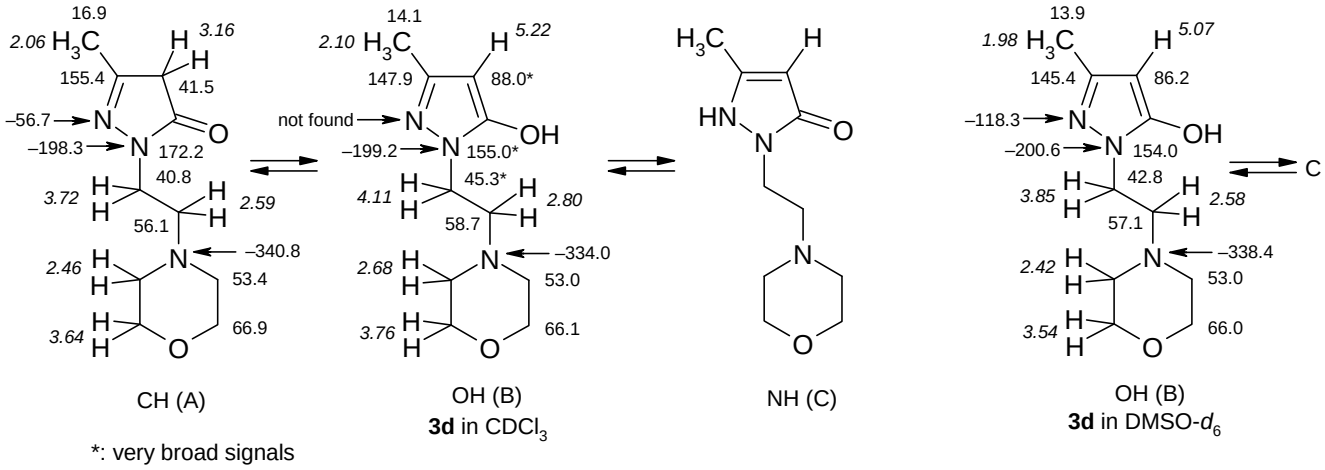


Figure 1. ^{1}H- (in italics), ^{13}C-, and ^{15}N-NMR (indicated by arrows) chemical shifts of **3d** (δ, ppm)

EXPERIMENTAL

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Finnigan MAT 8230 instrument (EI, 70 eV, HRMS). IR spectra were recorded on a Perkin-Elmer FTIR spectrum 1000 spectrophotometer. Elemental analyses were performed at the Microanalytical Laboratory, University of Vienna, using a Perkin-Elmer 2400 CHN Elemental Analyzer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C). The centre of the solvent signal was used as an internal standard which was related to TMS with δ = 7.26 ppm (^{1}H in $CDCl_3$), δ = 2.49 ppm (^{1}H in DMSO-d_6), δ = 77.0 ppm (^{13}C in $CDCl_3$), and δ = 39.5 ppm (^{13}C in DMSO-d_6). ^{15}N-NMR spectra were obtained on a Bruker Avance 500 instrument with a 'directly' detecting broadband observe probe and were referenced against external nitromethane (coaxial capillary). Systematic names according to IUPAC recommendations were generated with ACD/Name[21] and subsequently proved manually to ensure correct nomenclature within this publication.[22] Yields of products were not optimized.

General Procedure for the Synthesis of Hydrazines 2a–d.

To a well stirred solution of the corresponding aminoalkyl chloride • HCl (**1a**–**d**) (200 mmol) in H_2O (150 mL) was added solid K_2CO_3 (27.6 g, 200 mmol). Then the 'free base' was extracted with Et_2O (3 × 200 mL) and the combined organic layers were concentrated under reduced pressure. The remaining viscous oil was added dropwise to excess hydrazine monohydrate (70 mL) and then this mixture was refluxed for 1 h. With external cooling (ice bath), solid NaOH (40 g) was added and the formed yellow oil was extracted with THF[23] (3 × 150 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The remaining oil was subjected to vacuum distillation.

2-Hydrazino-*N,N*-dimethylethanamine (2a)

Yield: 7.9 g (38%); colourless liquid. Bp 83 °C / 57 mbar, (lit.,[24]: bp 94–96 °C / 83 mbar). ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 3.22 (br s, 3H, $N\underline{H}_2N\underline{H}$), 2.78 (t, ^3J = 6.0 Hz, 2H, H_3N_2-$C\underline{H}_2$), 2.36 (t, ^3J = 6.0 Hz, 2H, H_3N_2-$CH_2C\underline{H}_2$), 2.19 (s, 6H, Me_2N); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 57.2 (H_3N_2-$CH_2\underline{C}H_2$), 53.1 (H_3N_2-$\underline{C}H_2$), 45.5 (Me_2N); ^{15}N-NMR (50 MHz, $CDCl_3$): δ (ppm) −311.3 (NH_2), −318.3 (NH), −360.1 (Me_2N); MS (*m/z*, %): 58 (100).

3-Hydrazino-*N,N*-dimethylpropan-1-amine (2b)

Yield: 7.2 g (31%); colourless liquid. Bp 87 °C / 17 mbar, (lit.,[25]: bp 88–89 °C / 20 mbar). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 3.20 (br s, 3H, $N\underline{H}_2N\underline{H}$), 2.75 (t, ^3J = 6.9 Hz, 2H, H_3N_2-$C\underline{H}_2$), 2.26 (t, ^3J = 7.2 Hz, 2H, H_3N_2-$CH_2CH_2C\underline{H}_2$), 2.15 (s, 6H, Me_2N), 1.60 (m, 2H, H_3N_2-$CH_2C\underline{H}_2$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 57.7 (H_3N_2-$CH_2CH_2\underline{C}H_2$), 54.9 (H_3N_2-$\underline{C}H_2$), 45.4 (Me_2N), 25.7 (H_3N_2-$CH_2\underline{C}H_2$); ^{15}N-NMR (50 MHz, $CDCl_3$): δ (ppm) −309.5 (NH_2), −314.7 (NH), −355.2 (Me_2N); MS (*m/z*, %): 117 (M^+, 1), 58 (100).

1-(2-Hydrazinoethyl)piperidine (2c)

Yield: 6.4 g (22%); colourless liquid. Bp 113 °C / 16 mbar, (lit.,[26]: bp 113–115 °C / 16 mbar). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 3.26 (br s, 3H, $N\underline{H}_2N\underline{H}$), 2.82 (t, ^3J = 6.1 Hz, 2H, H_3N_2-$C\underline{H}_2$), 2.41 (t, ^3J = 6.1 Hz, 2H, H_3N_2-$CH_2C\underline{H}_2$), 2.34 (m, 4H, Pip H-2,6), 1.52 (m, 4H, Pip H-3,5), 1.39 (m, 2H, Pip H-4); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 57.0 (H_3N_2-$CH_2\underline{C}H_2$), 54.8 (Pip C-2,6), 52.6 (H_3N_2-$\underline{C}H_2$), 26.0 (Pip C-3,5), 24.3 (Pip C-4); ^{15}N-NMR (50 MHz, $CDCl_3$): δ (ppm) −310.6 (NH_2), −317.5 (NH), −336.1 (Pip-N); MS (*m/z*, %): 143 (M^+, 3), 98 (100).

4-(2-Hydrazinoethyl)morpholine (2d)

Yield: 17.4 g (60%); colourless liquid. Bp 131°C / 13 mbar, (lit.,[26]: bp 125 °C / 16 mbar). ^{1}H-NMR (500

MHz, $CDCl_3$): δ (ppm) 3.63 (m, 4H, Morph H-2,6), 3.18 (br s, 3H, $N\underline{H}_2N\underline{H}$), 2.79 (t, ^3J = 5.9 Hz, 2H, H_3N_2-$C\underline{H}_2$), 2.43 (t, ^3J = 5.9 Hz, 2H, H_3N_2-$CH_2C\underline{H}_2$), 2.37 (m, 4H, Morph H-3,5); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 66.8 (Morph C-2,6), 56.5 (H_3N_2-$CH_2\underline{C}H_2$), 53.7 (Morph C-3,5), 51.9 (H_3N_2-$\underline{C}H_2$); ^{15}N-NMR (50 MHz, $CDCl_3$): δ (ppm) −310.9 (NH_2), −318.4 (NH), −340.9 (Morph-N); MS (*m/z*, %): 145 (M^+, 5), 100 (100), 70 (12), 56 (26).

General Procedure for the Synthesis of 3a–d and 4b.

Method A: Keeping the temperature at ca. 0 °C with an external ice bath, to a mixture of alkylhydrazine (**2a**–**d**) (10 mmol), EtOH (5 mL), and 2 N HCl (0.5 mL) was added dropwise ethyl acetoacetate (for **3a**–**c**) (10 mmol) or ethyl benzoylacetate (for **4b**) (10 mmol). Stirring was continued at rt overnight. Evaporation of the solvents under reduced pressure afforded crude pyrazolones (**3a**–**c**, **4b**), which were recrystallized from the proper solvent given below.

Mehod B: A mixture of alkylhydrazine (**2c**–**d**) (10 mmol) and ethyl acetoacetate (for **3c**–**d**) (10 mmol) was stirred at rt overnight. Drying under reduced pressure afforded crude pyrazolones (**3c**–**d**), which were recrystallized from the proper solvent given below.

1-[2-Dimethylamino)ethyl]-3-methyl-1*H*-pyrazol-5-ol (3a)[27]

Yield (*method A*): 1.2 g (71%) of almost colorless crystals, mp 88–91 °C (toluene). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 11.40 (br s, 1H, OH), 5.16 (br s, 1H, H-4), 4.08 (br s, 2H, Pyr-$NC\underline{H}_2$), 2.76 (br s, 2H, Pyr-$NCH_2C\underline{H}_2$), 2.39 (br s, 6H, Me_2N), 2.06 (s, 3H, 3-Me); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 155.6 (C-5), 147.7 (C-3), 87.4 (C-4), 59.1 (Pyr-$NCH_2\underline{C}H_2$), 46.5 (Pyr-$N\underline{C}H_2$), 44.4 (Me_2N), 14.3 (3-Me); IR (KBr): ν (cm^{-1}) 1555; MS (*m/z*, %): 169 (M^+, 2), 58 (100). *Anal.* Calcd for $C_8H_{15}N_3O$: C, 56.78; H, 8.93; N, 24.83. Found: C, 56.90; H, 8.87; N, 24.65.

1-[3-(Dimethylamino)propyl]-3-methyl-1*H*-pyrazol-5-ol (3b)

Yield (*method A*): 1.7 g (93%) of a pale orange oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 9.64 (br s, 1H, OH), 5.09 (br s, 1H, H-4), 3.85 (br s, 2H, Pyr-$NC\underline{H}_2$), 2.36 (t, ^3J = 6.8 Hz, 2H, Pyr-$NCH_2CH_2C\underline{H}_2$), 2.26 (s, 6H, Me_2N), 2.05 (s, 3H, 3-Me), 1.89 (br s, 3H, Pyr-$NCH_2C\underline{H}_2$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 155.8 (br, C-5), 147.5 (br, C-3), 87.3 (br, C-4), 55.2 (br, Pyr-$NCH_2CH_2\underline{C}H_2$), 43.8 (br, Me_2N), 42.3 (Pyr-$N\underline{C}H_2$), 26.2 (Pyr-$NCH_2\underline{C}H_2$), 14.2 (br, 3-Me); IR (KBr): ν (cm^{-1}) 1548; MS (*m/z*, %): 183 (M^+, 5), 98 (19), 58 (100). HRMS Calcd for $C_9H_{17}N_3O$: 183.1372. Found: 183.1374.

3-Methyl-1-(2-piperidin-1-ylethyl)-1*H*-pyrazol-5-ol (3c)

Yield (*method B*): 2.0 g (96%) of pale orange crystals, mp 95–98 °C (petroleum ether–dichloromethane). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 12.66 (s, 1H, OH), 5.17 (s, 1H, H-4), 4.11 (m, 2H, Pyr-$NC\underline{H}_2$),

2.75 (m, 2H, Pyr-$NCH_2C\underline{H}_2$), 2.63 (m, 4H, Pip H-2,6), 2.08 (s, 3H, 3-Me), 1.68 (m, 4H, Pip H-3,5), 1.50 (2H, m, Pip H-4); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 155.9 (C-5), 147.7 (C-3), 87.1 (C-4), 58.7 (Pyr-$NCH_2\underline{C}H_2$), 53.9 (Pip C-2,6), 46.3 (Pyr-$N\underline{C}H_2$), 24.8 (Pip C-3,5), 23.3 (Pip C-4), 14.2 (3-Me); ^{15}N-NMR (50 MHz, $CDCl_3$): δ (ppm) −110.4 (N-2), −198.2 (N-1), −329.1 (Pip-N); IR (KBr): ν (cm^{-1}) 1558; MS (*m/z*, %): 209 (M^+, 3), 98 (100). ***Anal.*** Calcd for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.11; H, 8.97; N, 19.81.

3-Methyl-1-(2-morpholin-4-ylethyl)-1*H*-pyrazol-5-ol (3d)

Yield (*method B*): 1.9 g (90%) of pale orange crystals, mp 122–125 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): (ratio CH-Isomer to OH-Isomer 1.42:1): CH-isomer: δ (ppm) 3.72 (t, ^3J = 6.8 Hz, 2H, Pyr-$NC\underline{H}_2$), 3.64 (m, 4H, Morph H-2,6), 3.16 (s, 2H, H-4), 2.59 (t, ^3J = 6.8 Hz, 2H, Pyr-$NCH_2C\underline{H}_2$), 2.46 (br m, 4H, Morph H-3,5), 2.06 (s, 3H, 3-Me); OH-isomer: δ (ppm) 5.22 (s, 1H, H-4), 4.11 (m, 2H, Pyr-$NC\underline{H}_2$), 3.76 (m, 4H, Morph H-2,6), 2.80 (m, 2H, Pyr-$NCH_2C\underline{H}_2$), 2.68 (br m, 4H, Morph H-3,5), 2.10 (s, 3H, 3-Me); ^{1}H-NMR (300 MHz, DMSO-d_6): OH-isomer: δ (ppm) 7-14 (br s, 1H, OH), 5.07 (s, 1H, H-4), 3.85 (t, ^3J = 6.8 Hz, 2H, Pyr-$NC\underline{H}_2$), 3.54 (m, 4H, Morph H-2,6), 2.58 (t, ^3J = 6.8 Hz, 2H, Pyr-$NCH_2C\underline{H}_2$), 2.42 (m, 4H, Morph H-3,5), 1.98 (s, 3H, Me); ^{13}C-NMR (125 MHz, $CDCl_3$): (ratio CH-Isomer to OH-Isomer 1.42:1): CH-isomer: δ (ppm) 172.2 (C-5), 155.4 (C-3), 66.9 (Morph C-2,6), 56.1 (Pyr-$NCH_2\underline{C}H_2$), 53.4 (Morph C-3,5), 41.5 (C-4), 40.8 (Pyr-$N\underline{C}H_2$), 16.1 (3-Me); OH-isomer: δ (ppm) 155.0 (very br, C-5), 147.9 (C-3), 88.0 (C-4), 66.1 (Morph C-2,6), 58.7 (Pyr-$NCH_2\underline{C}H_2$), 53.0 (Morph C-3,5), 45.3 (very br, Pyr-$N\underline{C}H_2$), 14.1 (3-Me); ^{13}C-NMR (75 MHz, DMSO-d_6): OH-isomer: δ (ppm) 154.0 (C-5), 145.4 (C-3), 86.2 (C-4, ^1J (C4,H4) = 174.3 Hz), 66.0 (Morph C-2,6), 57.1 (Pyr-$NCH_2\underline{C}H_2$), 53.0 (Morph C-3,5), 42.8 (Pyr-$N\underline{C}H_2$), 13.9 (3-Me, ^1J (3-Me) = 126.7 Hz); ^{15}N-NMR (50 MHz, $CDCl_3$): CH-isomer: δ (ppm) −56.7 (N-2), −198.3 (N-1), −340.8 (Morph-N); OH-isomer: δ (ppm) −199.2 (N-1), −334.0 (Morph-N); N-2 not found; ^{15}N-NMR (50 MHz, DMSO-d_6): OH-isomer: δ (ppm) −118.3 (N-2), −200.6 (N-1), −338.4 (Morph-N); IR (KBr): ν (cm^{-1}) 1552; MS (*m/z*, %): 211 (M^+, 1), 100 (100). ***Anal.*** Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.92; H, 7.94; N, 19.88.

1-[3-(Dimethylamino)propyl]-3-phenyl-1*H*-pyrazol-5-ol (4b)

Yield (*method A*): 2.3 g (94%) of almost colorless crystals, mp 68–71 °C (petroleum ether–CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 8.07 (br s, 1H, OH), 7.71 (m, 2H, Ph-2,6), 7.34 (m, 2H, Ph-3,5), 7.25 (m, 1H, Ph-4), 5.71 (br s, 1H, H-4), 4.09 (br s, 2H, Pyr-$NC\underline{H}_2$), 2.43 (t, ^3J = 6.3 Hz, 2H, Pyr-$NCH_2CH_2C\underline{H}_2$), 2.34 (s, 6H, Me_2N), 2.04 (m, 2H, Pyr-$NCH_2C\underline{H}_2$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 156.0 (br, C-5), 150.0 (br, C-3), 134.2 (br, Ph C-1), 128.4 (Ph C-3,5), 127.3 (br, Ph C-4), 125.2 (Ph C-2,6), 84.9 (br, C-4), 55.0 (br, Pyr-$NCH_2CH_2\underline{C}H_2$), 43.6 ($Me_2N$), 43.0 (br, Pyr-$N\underline{C}H_2$), 26.4 (Pyr-

$NCH_2\underline{C}H_2$); ^{15}N-NMR (50 MHz, $CDCl_3$): δ (ppm) −193.3 (N-1), −349.8 (Me_2N); N-2 not found; IR (KBr): ν (cm^{-1}) 1566; MS (*m/z*, %): 245 (M^+, 5), 58 (100). *Anal.* Calcd for $C_{14}H_{19}N_3O$ • HCl: C, 59.67; H, 7.15; N, 14.91. Found: C, 59.49; H, 7.55; N, 15.25.

ACKNOWLEDGEMENTS

We are grateful to Dr. L. Jirovetz for recording the MS spectra.

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