A SYNTHETIC ENTRY TO 1- AND 2-AMINOPYRAZOLO[3,4-*d*]-1,2,3-TRIAZOLES

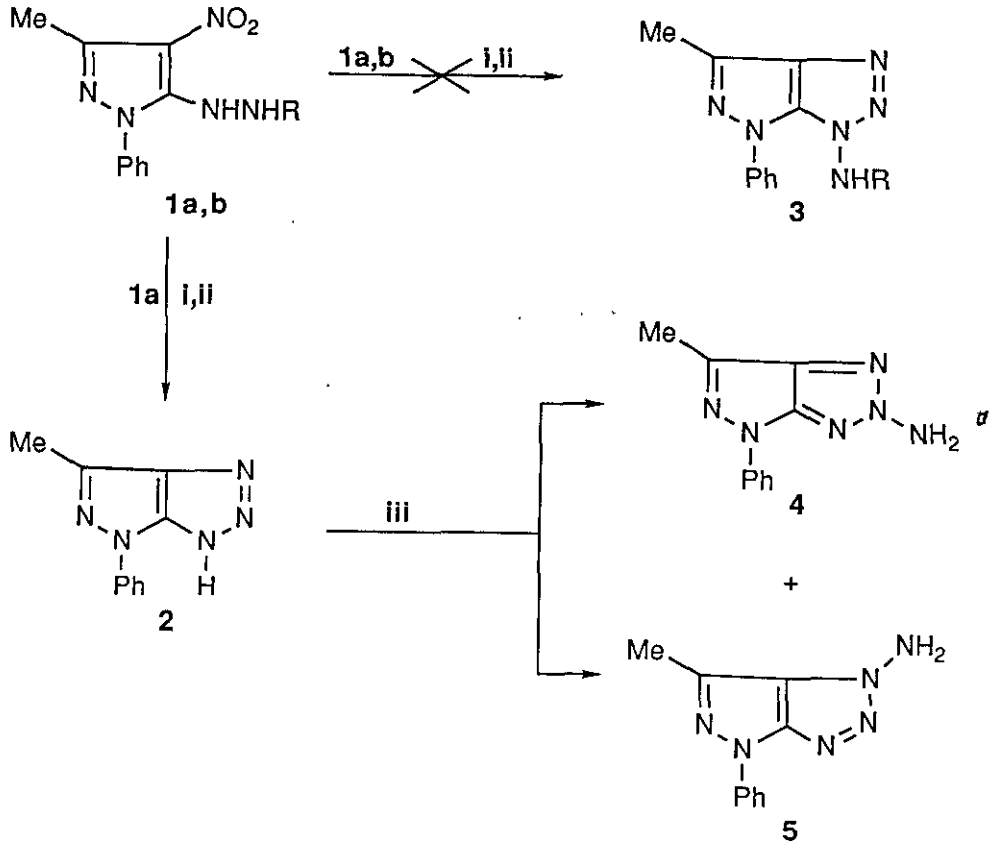
Chiara B. Vicentini,[a] Valeria Ferretti,[b] Augusto C. Veronese,[a] and Paolo Giori*[a]

[a]*Dipartimento di Scienze Farmaceutiche- Università di Ferrara*
44100 - FERRARA, Italy
[b]*Centro di Strutturistica Diffrattometrica- Università di Ferrara*
44100 - FERRARA, Italy

Abstract- 2-Aminopyrazolo[3,4-*d*]-1,2,3-triazole (**4**) and 1-aminopyrazolo[3,4-*d*]-1,2,3-triazole (**5**) were prepared by direct amination of pyrazolo[3,4-*d*]-1,2,3-triazole with hydroxylamine *O*-sulphonic acid in aqueous potassium hydroxide. The ratio of **4** to **5** was 2 : 3.

Annulated *N*-aminotriazoles are the subject of a large number of synthetic and biological studies mainly because of their proved ability to interfere with monooxygenase systems.[1] 1-Aminobenzotriazole (ABT) is the principal member of this class of compounds and can be prepared through cyclization of *o*-aminophenylhydrazine[2] or more conveniently by direct amination of benzotriazole.[2] It has been recognized that ABT is a cytochrome P-450-specific suicide substrate that leads to irreversible inactivation of the isozyme.[1]

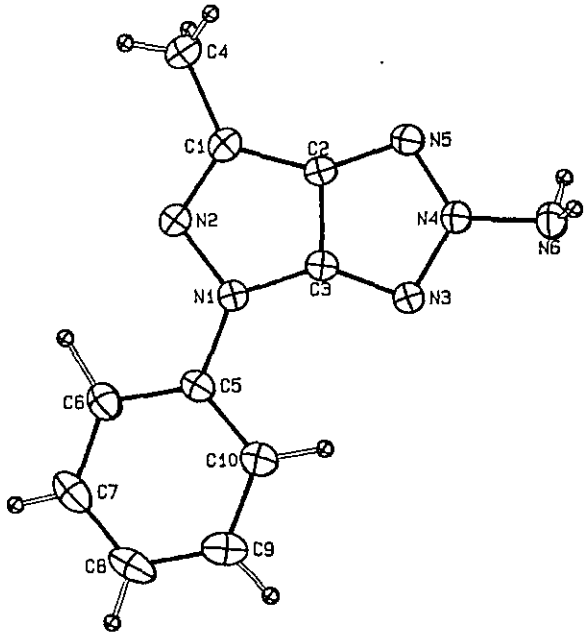
Despite the increasing biological significance of this class of compounds, no report has appeared concerning the synthesis of *N*-aminopyrazolotriazoles, which became the object of the present work. In unsymmetrical 1,2,3-triazoles, such as the target pyrazolo[3,4-*d*]-1,2,3-triazoles, three different positions of nitrogen substitution can be involved. Our first attempt was to prepare the 3-amino isomer by the classical procedure based on the use of *o*-aminohydrazino intermediates[2] (see Scheme). When the starting *N*-(3-methyl-4-nitro-1-phenyl-1*H*-pyrazol-5-yl)hydrazine[3] (**1a**) was submitted to catalytic hydrogenation followed by diazotization, the lone reaction product was the known pyrazolo[3,4-*d*]-1,2,3-triazole (**2**).[4,5] This result was explained by observing that the reduction product of nitropyrazolylhydrazine (**1a**) really was 4,5-diamino-3-methyl-1-phenylpyrazole.[4] No better results were obtained by protecting the hydrazine moiety of **1a** with an acyl group. Thus diazotization of *N*-(4-amino-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N'*-benzoylhydrazine, prepared by catalytic reduction of the corresponding 4-nitro derivative (**1b**),[6] afforded a red brown cake which could not be purified even by chromatographic techniques.



R: a=H; b=COC_6H_5
(i) H_2/5%Pt-C; (ii) NO^+; (iii) H_2NOSO_3H/OH^-

Scheme

After these unsuccessful attempts, we decided to apply the Campbell procedure for the direct amination of benzotriazole.[2] The 6-methyl-4-phenylpyrazolo[3,4-*d*]-1,2,3-triazole (**2**)[4,5] was treated with hydroxylamine *O*-sulphonic acid in aqueous potassium hydroxide at 70-75°C. The flash chromatography of the reaction product gave two compounds which were characterized as 2-amino-6-methyl-4-phenylpyrazolo[3,4-*d*]-1,2,3-triazole (**4**) and 1-amino-6-methyl-4-phenylpyrazolo[3,4-*d*]-1,2,3-triazole (**5**). The ratio of **4** to **5** was about 2 : 3. No trace of the 3-amino isomer was detected. The optimum yield (*ca.* 45%) in aminated products was obtained using 5 equivalents of potassium hydroxide and 2 equivalents of hydroxylamine-*O*-sulphonic acid for 1 equivalent of pyrazolotriazole (**2**).[7] The spectroscopic data (ir, ^{1}H nmr and ^{13}C nmr)[8] agreed with the proposed structures, but did not allow an unequivocal assignment. For this reason both compounds were submitted to X-ray crystallographic analysis[9] which consented to assess that the minor product was the 2-amino isomer (**4**) and the major product was the 1-amino isomer (**5**).



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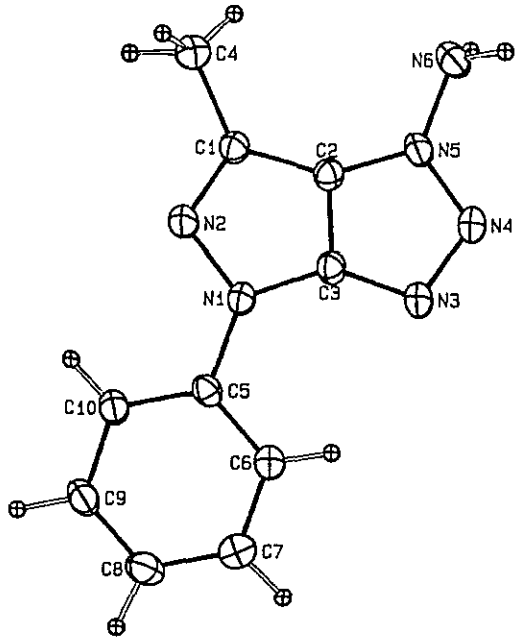

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ORTEP[10] views of molecules (**4**) and (**5**) showing the termal ellipsoids at 30% probability.

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7. 6-Methyl-4-phenylpyrazolo[3,4-*d*]-1,2,3-triazole (**2**)[4,5] (0.1 mol) was dissolved in a solution of potassium hydroxide (1.5 mol) in water (100 ml) at 60°C. Solid hydroxylamine-*O*-sulphonic acid (0.2 mol) was added portionwise during 1 h, the temperature being maintained at 70-75°C. The mixture was stirred for 1 h at *ca.* 70°C, cooled and filtered. The precipitate was washed with water and the residue was dissolved in ethyl acetate, washed with aqueous potassium hydroxide, dried over anhydrous magnesium sulfate and evaporated. The flash chromatography of the resulting solid (silica gel 230-400 mesh, eluent: 3:7 ethyl acetate/petroleum ether) allowed the separation of two products: the 2-amino-6-methyl-4-phenylpyrazolo[3,4-*d*]-1,2,3-triazole (**4**) (yield 18 %, mp 138-139°C, Rf=0.45) and the 1-amino-6-methyl-4-phenylpyrazolo[3,4-*d*]-1,2,3-triazole (**5**) (yield 27 %, mp 183°C, Rf=0.26).

8. **4**: Ir (KBr) 3300, 1600, 1580 br, 1550, 1500 cm^{-1}, ^1H nmr (CDCl3) δ: 2.55 (s, 3H, Me), 6.40 (br, 2H, NH_2), 7.15 (m, 1H, Ph), 7.43 (m, 2H, Ph), 7.84 (m, 2H, Ph); ^{13}C nmr (CDCl3) δ: 12.79 (q, J= 128.2 Hz, Me), 116.15 (d, J=152.2 Hz, Ph), 124.02 (d, J=161.8 Hz, Ph), 129.37 (d, J=158.3 Hz, Ph), 135.83 (s, C-6), 138.10 (s, C-6a), 138.82 (s, Ph), 150.02 (s, C-3a). **5**: Ir (KBr) 3300, 3190, 1650 br, 1600, 1560, 1500 cm^{-1}, ^1H nmr (DMSO-d6) δ: 2.51 (s, 3H, Me), 3.40 (br, 2H, NH_2), 7.23 (m, 1H, Ph), 7.54 (m, 2H, Ph), 7.96 (m, 2H, Ph); ^{13}C nmr (DMSO-d6) δ: 11.57 (q, J=129.2 Hz, Me), 115.33 (d, J=159.4 Hz, Ph), 124.05 (d, J=163.5 Hz, Ph), 126.96 (s, C-6a), 129.10 (s, C-6), 129.18 (d, J=160.1 Hz, Ph), 138.04 (s, Ph), 155.26 (s, C-3a).

9. X-Ray crystallographic analyses were carried out on an Enraf-Nonius CAD4 diffractometer with monochromated MoKα radiation and ω/2θ scan technique. 1246 and 2139 independent reflections were collected for compounds (**4**) and (**5**), respectively, and both the structures were solved by direct methods (M.C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna, and D. Viterbo, 'SIR88. A Direct Methods Program for the automatic Solution of Crystal Structures. *J. Appl. Cryst.*, 1989, **22**, 389). Crystal data for **4**: $C_{10}H_{10}N_6$, F.W.= 214.23, monoclinic, space group Cc (N. 9), *a*=11.002(2) Å, *b*= 14.090(1) Å, *c*= 6.758(2) Å, β= 101.69(2)°, V=1025.9 $Å^3$, Z=4, D_{calc}= 1.387 g/cm^3, μ(Mokα)= 0.87 cm^{-1}, R= 0.036, Rw= 0.044, 1092 observed reflections [I>3σ(I)] used in the refinement (*'MolEN, an Interactive Structure Solution Procedure'*, Enraf-Nonius, Delft, The Netherlands, 1990). Crystal data for **5**: $C_{10}H_{10}N_6$, F.W.= 214.23, monoclinic, space group $P2_1/n$ (N. 14), *a*= 7.158(2) Å, *b*= 10.371(3) Å, *c*= 13.628(3) Å, β= 103.35(2)°, V=984.3 $Å^3$, Z=4, D_{calc}= 1.446 g/cm^3, μ(Mokα)= 0.91 cm^{-1}, R= 0.052, Rw= 0.063, 1208 observed reflections [I>3σ(I)] used in the refinement (*'MolEN, An Interactive Structure Solution Procedure'*, Enraf-Nonius, Delft, The Netherlands, 1990).

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