

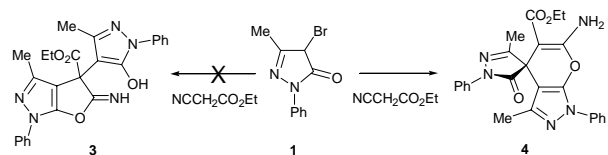
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Structural reassignment of an “unusual” derivative of 3-methyl-5-phenylpyrazol-5-one (Edaravone)

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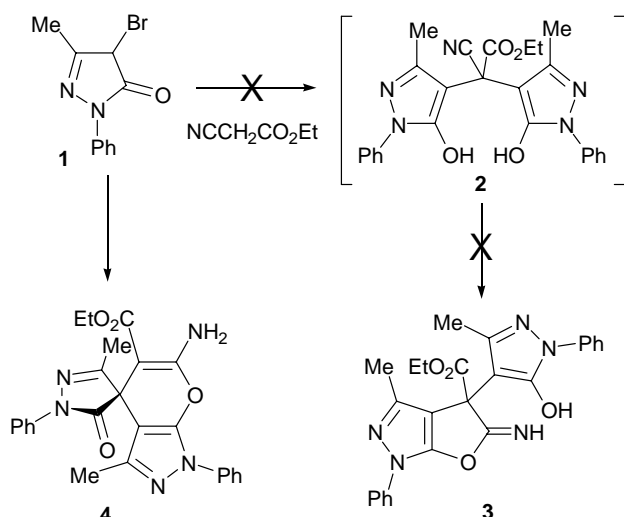
Jennifer Burgess and Peter J. Steel*

Department of Chemistry, University of Canterbury, Christchurch, New Zealand

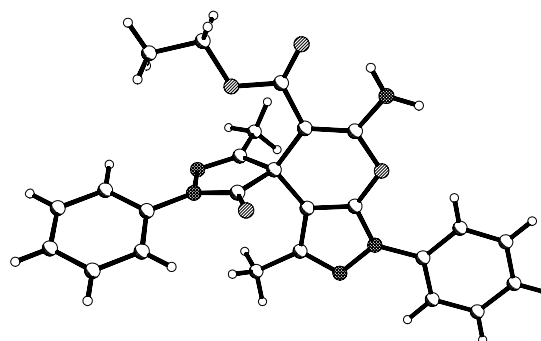
Abstract— The structure of the major product from reaction of 4-bromo-3-methyl-1-phenylpyrazol-5-one (**1**) with ethyl cyanoacetate is shown, by means of an X-ray crystal structure determination, to be the spirocyclic compound **4**, rather than the previously proposed isomer **3**. © 2007 Elsevier Science. All rights reserved

The chemistry of derivatives of 3-methyl-1-phenylpyrazol-5-one (Edaravone)¹ has been the subject of much study, as has that of the *N*-methyl derivative antipyrine, the first truly synthetic pain reliever.² Recently,³ it was claimed that the 4-bromo derivative **1** reacted with ethyl cyanoacetate to produce, as the major product, the “unusual” furanopyrazole **3**, supposedly via the intermediacy of the symmetrical compound **2** (Scheme 1). We had reason to question the validity of this claim and now show unambiguously, using X-ray crystallography, that this reaction product is actually the spirocyclic isomer **4**.

We have resynthesized this compound,⁴ which directly furnished crystals suitable for single crystal X-ray structure determination from the crude reaction mixture. The infrared and ¹H NMR spectra matched the reported values. It crystallizes in the monoclinic space group P2₁/*n*, with a single molecule in the asymmetric unit.⁵ Figure 1 shows a perspective view of the structure, which reveals that it is actually a spiro[(pyrano[2,3-*c*]pyrazole)-4,4'-pyrazoline], rather than the previously proposed structure. This is a known heterocyclic ring system that has been previously reported in other derivatives of similar pyrazolones.⁶



Scheme 1.

Figure 1. Perspective view of the X-ray structure of **4**.

Thus, the two exchangeable protons in the NMR spectrum are associated with the enamino group, rather than imine and hydroxyl protons. In the solid state, one of the NH₂ hydrogens is involved in an intramolecular hydrogen bond to the adjacent ester carbonyl oxygen, while the other participates in an intermolecular hydrogen bond to the spiropyrazolidinone oxygen atom of an adjacent molecule related by a crystallographic centre of inversion. The molecular packing also involves extensive π–π stacking interactions between adjacent molecules.

Keywords: Pyrazolone, Spiro compound, Crystal structure

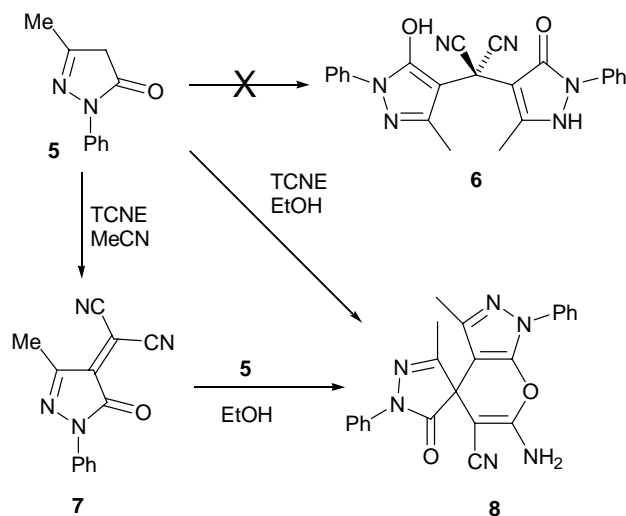
Corresponding author: Tel.: +64-3-3642432; fax: +64-3-3642110; email: peter.steel@canterbury.ac.nz

Within the structure the pyranopyrazole ring system is approximately orthogonal (88.7°) to the other pyrazole ring, as expected for a spiro centre. The planes of the *N*-phenyl rings are inclined to the planes of the attached pyranopyrazole and pyrazoline rings at angles of 6.8 and 25.0° , respectively. These features and the bond lengths and angles are similar to those in the only other reported X-ray crystal structure of this spirocyclic ring system.⁷

In retrospect, the formation of this product is not totally unexpected as we have previously demonstrated,⁷ as part of a long-standing interest in the chemistry and tautomerism of pyrazolones,⁸ that the product of reaction of 3-methyl-1-phenylpyrazol-5-one (**5**) with TCNE is the related compound **8**, rather than the previously proposed isomer **6**, formed via the intermediate **7** (Scheme 2). In the present case a related mechanism is likely for formation of **4**.

In conclusion, we have shown that the “unusual” major product from the reaction of 4-bromo-3-methyl-1-phenylpyrazol-5-one (**1**) with ethyl cyanoacetate is actually the spirocyclic compound **4**, rather than the previously proposed isomer **3**.

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Scheme 2.

References and notes

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- Preparation of 4*: A solution of **1** (0.253 g, 1.0 mmole), ethyl cyanoacetate (1 mL, 9mmole) and 4 drops of piperidine in ethanol (15 mL) was refluxed for 5 hr. Colourless crystals of the product were deposited, which were isolated by filtration and washed with methanol. Yield 84 mg (17%). M.p. 232-3 °C (dec). IR(KBr) 1641, 1686 cm^{-1} . ^1H NMR (DMSO) δ : 0.97 (3H, t, OCH_2CH_3), 1.97 (3H, s, CH_3), 2.03 (3H, s, CH_3), 4.03 (2H, q, OCH_2CH_3), 7.31 (1H, t, *para*-H), 7.47 (1H, t, *para*-H), 7.56 (2H, t, *meta*-H), 7.63 (2H, t, *meta*-H), 7.93 (2H, d, *ortho*-H), 7.97 (2H, d, *ortho*-H), 8.56 (1H, s, NH). It was also obtained in 87% yield from reaction of cyanoacetamide with **1** in refluxing ethanol, in the presence of a trace of piperidine.
- Crystal Data for 4 at 93 K*. $\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}_4$, *M* 457.48, monoclinic, space group $P2_1/n$, *a* 12.9759(16), *b* 12.2404(15), *c* 15.3058(19) Å, β 113.038(2)°, *V* 2237.1(5) Å³, *F*(000) 960, *D*_c(*Z*=4) 1.358 g cm^{-3} , $\mu(\text{Mo K}\alpha)$ 0.95 cm^{-1} , crystal dimensions 0.55 x 0.44 x 0.09 mm, $2\theta_{\text{max}}$ 53°, *wR* (all 4505 data) 0.0856, conventional *R* (3301 data with $I > 2\sigma(I)$) 0.0364. Complete crystallographic data, as a CIF file, have been deposited with the Cambridge Crystallographic Data Centre (CCDC No 297340). Copies can be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (e-mail: deposit@ccdc.cam.ac.uk).
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