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# 4,5-Dihydro-3-methyl-5-(4-methylphenyl)-1*H*-pyrazole-1-carboxamide[1]

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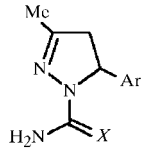
The reaction between 4-(4-methylphenyl)but-3-en-2-one and aminoguanidine produced an unexpected product of formula $C_{12}H_{15}N_3O$, consisting of a carboxamide moiety joined to a substituted pyrazoline ring at one of the N atoms. The pyrazoline ring adopts a flat-envelope conformation and the substituted phenyl ring is oriented almost perpendicular to the heterocycle. The carbonyl O atom has partial anionic character as a result of the transfer of $\pi$ density from the two adjacent $sp^2$ N atoms and is involved in an intermolecular hydrogen bond with the amide group.

## Comment

In a search for new inhibitors of nitric oxide (NO) synthase, we have found that cyclocondensation of 4-(2-hydroxyphenyl)but-3-en-2-one with aminoguanidine affords 4,5-dihydro-5-(2-hydroxyphenyl)-3-methyl-1*H*-pyrazole-1-carboximidamide, (I*a*), as the sole product. In contrast, analogous heterocyclization of both 4-phenyl- and 4-(4-methylphenyl)-but-3-en-2-one gave rise to two products, of which the corresponding amidines, *viz.* (I*b*) and (I*c*), were easily identified. In the latter two cases, the compounds isolated were identified as 5-aryl-4,5-dihydro-3-methyl-1*H*-pyrazole-1-carboxamides (II*b*) and (II*c*), which probably arose from the target amidines (I*b*) and (I*c*) by hydrolysis (Světlík & Sallai, 2002). However, since the NMR spectra of the resultant heterocycles are almost identical, it is desirable to determine the structure of the carboxamides. A further aim of this structure determination was to establish the spatial distribution of the pharmacophoric groups for subsequent use in an analysis of structure–activity relationships. In this communication, we report the structure of (II*c*).

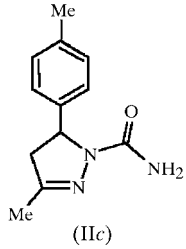
The molecular structure and the atom-numbering scheme of (II*c*) are shown in Fig. 1. As can be seen, the compound is indeed the hydrolytic product of (I*c*), *i.e.* (II*c*) consists of a substituted pyrazoline ring and a carboxamide function attached to atom N1.

As mentioned above, the main purpose of this structure determination was to establish the relative three-dimensional disposition of the putative pharmacophoric elements [phenyl ring(s) and hydrogen-bond donor and acceptor] that are responsible for binding a compound to the NO synthase (Griffith & Gross, 1996). Obviously, the disposition of these structural elements depends primarily on the conformation of the central heterocycle. The pyrazoline ring adopts a flat-envelope conformation, with atom C5 on the flap; the deviation of the out-of-plane atom from the mean plane of the remaining four atoms [r.m.s. deviation 0.005 (2) Å] is 0.329 (3) Å. The 4-methylphenyl group occupies a pseudo-axial position and, as a result, is approximately perpendicular to the mean plane of the pyrazoline ring [dihedral angle = 78.8 (2)°]. The phenyl ring is rotated about the exocyclic C5—C6 bond in such a manner that the N1—C5—C6—C11 torsion angle is −19.7 (3)°.




(*a*) Ar = 2-OHC$_6$H$_4$
(*b*) Ar = C$_6$H$_5$
(*c*) Ar = 4-MeC$_6$H$_4$

(I*a*–*c*) *X* = NH (II*b*,*c*) *X* = O




(II*c*)

Selected bond lengths and angles in the molecule are listed in Table 1. As expected, atom N1 is $sp^2$ hybridized, as evidenced by the sum of the valence angles around it [357.9 (1)°], with the lone-pair electrons available for $\pi$ bonding. It has been reported (Krishna *et al.*, 1999) that the N—N bond length in the pyrazoline ring varies over a wide range, from 1.234 (8) to 1.385 (4) Å, where the length depends on the substituents bonded to the N atoms; accordingly, the length of the adjacent C=N bond ranges from 1.288 (4) to 1.461 (8) Å. These differences are caused by a varying degree of conjugation in the $\pi$-electron portion of the pyrazoline ring, which is sensitive to the nature of the substituent(s) bonded to the atoms of the $\pi$ system. The N1—N2 bond length of 1.393 (3) Å found in the present derivative further extends this range, approximating the length of a pure single bond (1.41 Å; Burke-Laing & Laing, 1976). Similarly, the corresponding N2=C3 bond [1.281 (3) Å] has the character of a pure double bond (1.27 Å). That the lone-pair electrons on atom N1 are delocalized through conjugation with the carboxamide group rather than the N2=C3 double bond is also seen in the N1—C14 bond length [1.363 (3) Å], which is intermediate between single- and double-bond values. However, $\pi$-electron delocalization from the exocyclic amide

[1] Dedicated to Dr Vladimír Hanuš on the occasion of his 80th birthday.

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N atom into the C14—O1 carbonyl bond is even more pronounced, as reflected in the C14—N3 bond length [1.335 (3) Å], which is ∼0.03 Å shorter than the N1—C14 bond and is comparable to the values typically found in amides (Benedetti *et al.*, 1983). Owing to the transfer of the $\pi$ density from 'both' sides of the carbonyl group, atom O1 has partial anionic character, as shown by the lengthening of the C═O bond [1.252 (3) Å] relative to that normally found for amides; as a result, atom O1 should have an increased capacity to function as a hydrogen-bond acceptor. Other bond distances and angles in the remaining parts of the molecule are close to generally expected values.

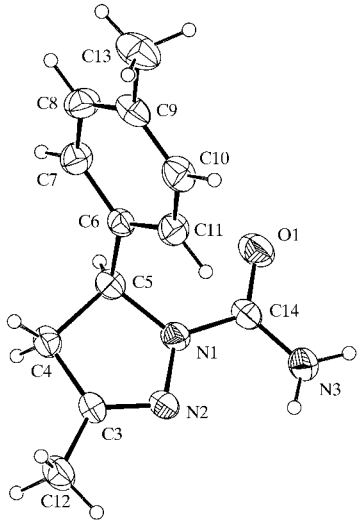


**Figure 1**
Displacement ellipsoid plot of (II*c*), with the labelling scheme for the non-H atoms, which are drawn as 35% probability ellipsoids.

The enhanced ability of carbonyl atom O1 as a hydrogen-bond acceptor is reflected in the crystal packing, which is dominated by a pair of hydrogen bonds that join neighboring molecules related by a center of symmetry [N3—H3···O1($1-x, 2-y, 1-z$): N···O = 2.898 (3) Å, H···O = 2.05 Å and N—H···O = 169°]. This self-complementary interaction aggregates molecules into pairs, which are loosely packed in the extended structure through van der Waals interactions with surrounding pairs.

*Crystal data*

$C_{12}H_{15}N_3O$
$M_r$ = 217.27
Triclinic, $P\overline{1}$
$a$ = 6.080 (3) Å
$b$ = 6.815 (3) Å
$c$ = 14.314 (5) Å
$\alpha$ = 96.86 (4)°
$\beta$ = 91.28 (4)°
$\gamma$ = 101.40 (5)°
$V$ = 576.6 (4) Å$^3$
$Z$ = 2
$D_x$ = 1.251 Mg m$^{-3}$
$D_m$ = 1.25 (1) Mg m$^{-3}$
$D_m$ measured by flotation in bromoform/cyclohexane
Mo $K\alpha$ radiation
Cell parameters from 15 reflections
$\theta$ = 7–18°
$\mu$ = 0.08 mm$^{-1}$
$T$ = 293 (2) K
Prism, colourless
0.35 × 0.30 × 0.25 mm

*Data collection*

Syntex $P2_1$ diffractometer
$\theta/2\theta$ scans
2041 measured reflections
2041 independent reflections
1276 reflections with $I > 2\sigma(I)$
$\theta_{max}$ = 25.1°
$h = -5 \rightarrow 7$
$k = -5 \rightarrow 8$
$l = -17 \rightarrow 16$
2 standard reflections
every 98 reflections
intensity decay: 2%

*Refinement*

Refinement on $F^2$
$R(F)$ = 0.052
$wR(F^2)$ = 0.146
$S$ = 1.02
2041 reflections
147 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0821P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.20 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.20 e Å$^{-3}$

**Table 1**
Selected geometric parameters (Å, °).

| | | | |
|---|---|---|---|
| N1—C14 | 1.363 (3) | C4—C5 | 1.536 (3) |
| N1—N2 | 1.393 (3) | C5—C6 | 1.510 (3) |
| N1—C5 | 1.460 (3) | C14—O1 | 1.252 (3) |
| N2—C3 | 1.281 (3) | C14—N3 | 1.335 (3) |
| C3—C4 | 1.482 (3) | | |
| | | | |
| C14—N1—N2 | 121.44 (19) | N1—C5—C6 | 113.05 (18) |
| C14—N1—C5 | 123.52 (19) | N1—C5—C4 | 99.65 (17) |
| N2—N1—C5 | 112.97 (17) | C6—C5—C4 | 112.64 (18) |
| C3—N2—N1 | 106.45 (18) | O1—C14—N3 | 122.9 (2) |
| N2—C3—C4 | 114.5 (2) | O1—C14—N1 | 120.5 (2) |
| C3—C4—C5 | 102.04 (18) | N3—C14—N1 | 116.6 (2) |
| | | | |
| C14—N1—N2—C3 | 177.32 (19) | C3—C4—C5—N1 | 18.7 (2) |
| C5—N1—N2—C3 | 13.1 (2) | N1—C5—C6—C11 | −19.7 (3) |
| N1—N2—C3—C4 | 1.3 (2) | N2—N1—C14—O1 | −175.2 (2) |
| N2—C3—C4—C5 | −13.7 (3) | N2—N1—C14—N3 | 6.1 (3) |

## Experimental

Compound (II*c*) was synthesized by cyclocondensation of 4-(4-methylphenyl)but-3-en-2-one with aminoguanidine hydrogencarbonate according to the method of Světlík & Sallai (2002). Briefly, a suspension of both reactants (10 mmol each) in *n*-butanol (30 ml) was stirred under reflux for 3 h. The resulting solution was concentrated on a vacuum rotary evaporator, and the syrupy residue obtained was dissolved in ethyl acetate (10 ml) and left to stand at room temperature. The crystalline material that appeared was collected by filtration and recrystallized from dioxane (yield 0.27 g, 26%; m.p. 471–473 K).

H atoms were allowed for as riding on their carrier atoms, with $U_{iso}$ values set at 1.2 (1.5 for methyl H atoms) times the $U_{eq}$ values of the parent atoms.

Data collection: *Syntex P2*$_1$ *Diffractometer Software* (Syntex, 1973); cell refinement: *Syntex P2*$_1$ *Diffractometer Software*; data reduction: *XP*21 (Pavelčík, 1987); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA1020). Services for accessing these data are described at the back of the journal.

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