Formation and Structure of 1-Amino-4-methyl-4-(4-methyl-5-phenyl-1*H*-pyrazol-3-ylamino)-3-phenyl-4,5-dihydro-1*H*-pyrazol-5-one

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Received October 6, 1997

The title compound **3** was obtained during the rearrangement of isoxazol-5-yl hydrazine **1** to 1-aminopyrazolone **2** at 115°. X-ray analysis of the corresponding benzylidene derivative allowed us to achieve the structure assignment.

J. Heterocyclic Chem., **35**, 109 (1998).

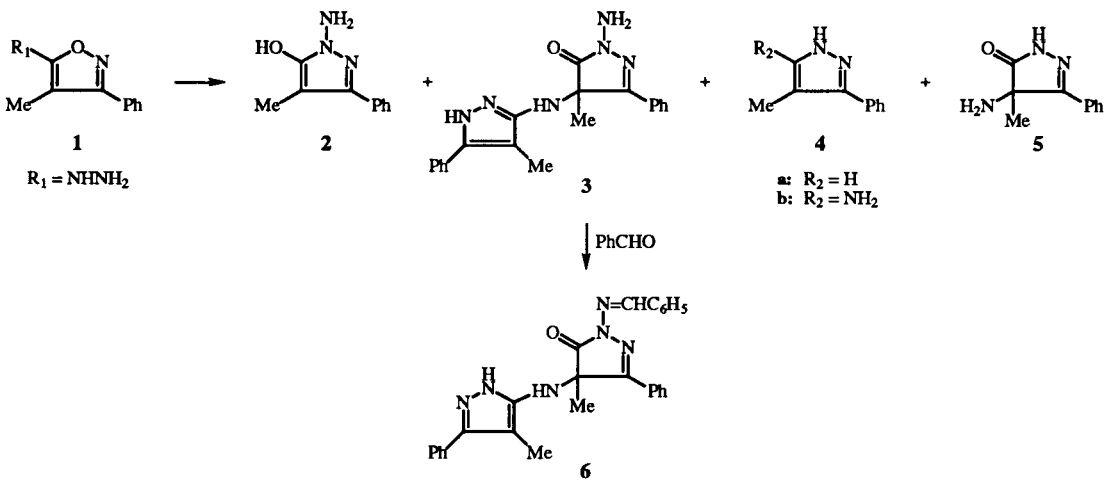
Several years ago we investigated thermal [1] and photochemical [2] behaviour of isoxazol-5-ylhydrazines: isomerizations to 1-amino-, 3-methylamino- or 4-amino-2-pyrazolin-5-ones, tetrahydro-1,2,4-triazin-6-ones or 1*H*-azirines were observed, depending on the nature of the substrate and on the reaction conditions.

Afterwards, in view of the interest for the investigation of the chemical and biological properties of 1-amino-2-pyrazolin-5-ones [3,4], we repeated the preparation of these compounds and we noticed that the rearrangement of 4-methyl-3-phenylisoxazol-5-yl hydrazine in hydrazine is temperature-dependent. In fact, reduced yields of the expected pyrazolone **2** were found when the reaction was carried out at 115° instead of 100° [1] and some (20-25%) alkali insoluble material was obtained. Crystallisation of this crude mixture from ethanol gave a pure compound (tlc) with a molecular formula of $C_{20}H_{20}N_6O$, mp 242°, which by condensation with benzaldehyde gave the corresponding monobenzylideneamino derivative. Infrared and nmr data of this product were consistent with the presence of a NH_2, of two NH groups, of an amidic carbonyl group, of two types of methyl and phenyl substituents and of five quaternary carbons, probably belonging to heterocyclic systems. In particular, it is to be noted in the ^{13}C nmr spectrum a signal at 62.3 ppm, attributable to a strongly deshielded sp^3 quaternary carbon. Electron impact mass spectrum (Experimental) of **3** in the low mass region (m/z < 173) and of 5(3)-amino-4-methyl-3(5)-phenylpyrazole (M^+ = 173) are very similar, strongly suggesting that this system is a part of the structure of the compound melting at 242°. However, these indications are insufficient for a final conclusion about the configuration of this product. Fortunately, well formed crystals, suitable for X-ray crystallographic analysis, were obtained from the corresponding benzylideneamino derivative. In this way, it was possible to assign structure **6** to this compound (Figure 1) and consequently, structure **3** to the precursor melting at 242° (Scheme I).

So far as the solid state structure of **6** is concerned, the pyrazole ring appears perfectly planar (maximum deviation 0.008 Å of C7 from least square plane); the pyrazolone ring takes an envelop conformation very slightly puckered being the distance of C4 from the least square plane through C3-N2-N1-C5-O1 0.145 Å. The phenyl rings bonded to the pyrazole and to the pyrazolone rings are twisted in respect to the heterocyclic ring of 13.49(1)° and 14.3(1)° respectively.

As shown in the figure, the methyl group on the pyrazole ring and the phenyl group of the benzal moiety are disordered at two sites with the same occupation factor. The phenyl ring

Scheme I



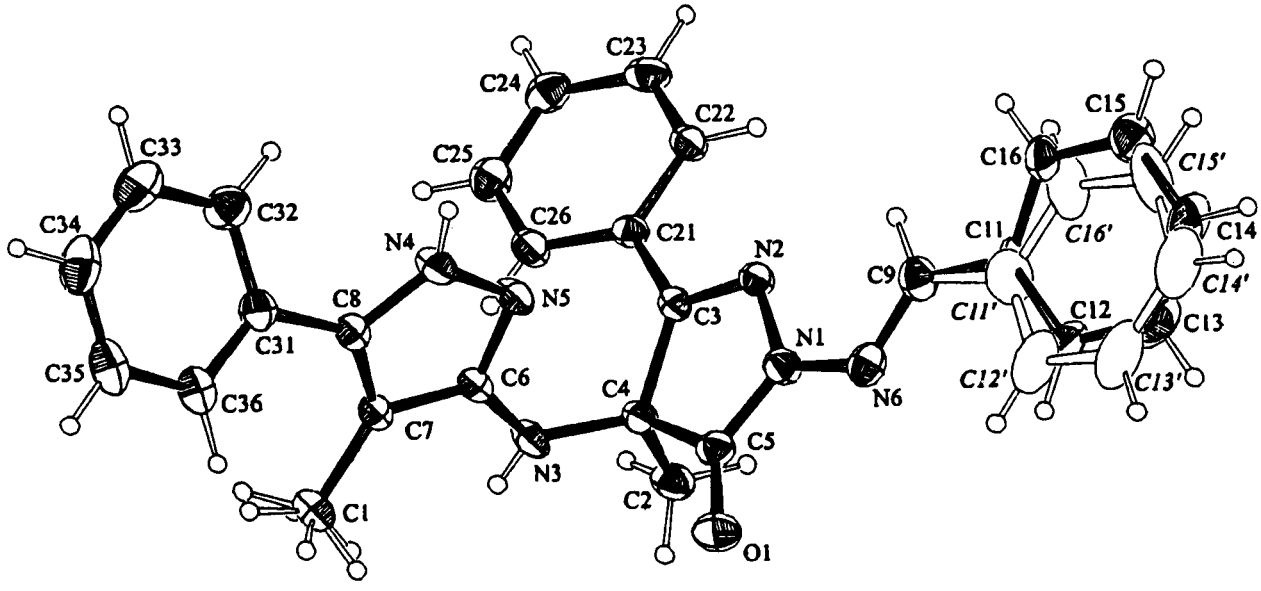


Figure 1. Ortep view of compound **6**, with 50% probability thermal ellipsoids, showing the disordered methyl group and phenyl ring.

is roughly coplanar with the benzal moiety (torsion angle C12'-C11'-C9-N6 = -4.0(3)° in one site; in the other it is twisted with a torsion angle C12-C11-C9-N6 = 17.0(3)°. An hydrogen bond is observed between the hydrogen atom bonded to N3 and the N5 of the pyrazole ring of the molecule related by the symmetry operation: x, 1.5-y, -0.5+ z.

The alkali insoluble fraction of the above described rearrangement contained, in addition to the expected 4-aminopyrazolone **5** [1], the pyrazole **4a** and the aminopyrazole **4b**. It is to be underlined that **4b** is not an intermediate to **3**, since it did not gave this compound by reaction with the 1-aminopyrazolone **2** at 115° in hydrazine. A possible rationale for the above *anomalous* rearrangement of **1** involves competition, in dependence on the temperature of the reaction, between omolytic opening of N-O and N-N bond. The first process is responsible of the *normal* formation of pyrazolones **2** and **5** [1], the second gives (Scheme II) an isoxazole-NH radical which can afford the aminoisoxazole **8** by hydrogen abstraction from the solvent or can attack the anion of the 1-aminopyrazolone **2** to give the intermediate **7**. This latter type of reaction reminds one of the previously reported formation of 4-hydroxy or 4-amino derivatives from 2-pyrazolin-5-ones under basic conditions [5]. As expected, both the isoxazole intermediates **7** and **8**, under the reaction conditions (strong excess of

Scheme II

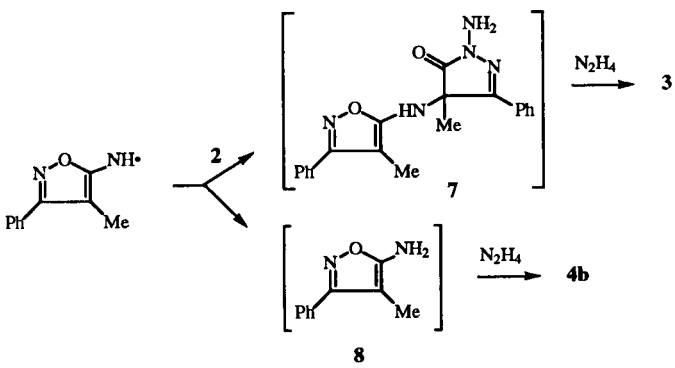


Table 1

Crystal Data and Structure Refinement for Compound **6**

Identification code	Compound **6**
Empirical formula	$C_{27}H_{24}N_6O$
Formula weight	448.52
Temperature	293(2) °K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P\,2_1/c$
Unit cell dimensions	a = 9.744 (1) Å α = 90°
	b = 24.079(2) Å β = 111.82(1)°
	c = 10.374(1) Å γ = 90°
Volume	2259.6(4) Å^3
Z	4
Density (calculated)	1.318 Mg/m^3
Absorption coefficient	0.084 mm^{-1}
F(000)	944
Crystal size	0.4 x 0.3 x 0.3 mm
θ range for data collection	1.69 to 25.00°
Index ranges	-11<=h<=11, -28<=k<=28,
	-12<=l<=12
Reflections collected	8435
Independent reflections	3981 [R(int) = 0.0292]
Refinement method	Full-matrix-block least-squares on F^2
Data / restraints / parameters	3979 / 0 / 377
Goodness-of-fit on F^2	0.918
Final R indices [I>2s(I)]	R1 = 0.0445, wR2 = 0.1211
R indices (all data)	R1 = 0.0772, wR2 = 0.1483
Largest diff. peak and hole	0.237 and -0.182 e. Å^{-3}

Table 2

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for Compound **6**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

	x	y	z	U(eq)
O(1)	1287(2)	6266(1)	1905(2)	59(1)
N(1)	3041(2)	6374(1)	4124(2)	40(1)
N(2)	4221(2)	6734(1)	4836(2)	36(1)
N(3)	2417(2)	7398(1)	1644(2)	43(1)
N(4)	890(2)	8190(1)	3551(2)	45(1)
N(5)	1831(2)	7780(1)	3483(2)	44(1)
N(6)	2570(2)	5966(1)	4794(2)	45(1)
C(1)	-76(3)	8195(1)	-209(2)	48(1)
C(2)	4195(3)	6680(1)	1687(2)	48(1)
C(3)	4360(2)	7080(1)	3944(2)	32(1)
C(4)	3299(2)	6953(1)	2466(2)	36(1)
C(5)	2366(2)	6494(1)	2748(2)	41(1)
C(6)	1601(2)	7757(1)	2133(2)	35(1)
C(7)	524(2)	8138(1)	1341(2)	36(1)
C(8)	103(2)	8417(1)	2297(2)	37(1)
C(9)	3221(3)	5937(1)	6109(3)	48(1)
C(11)	2892(4)	5538(1)	7014(3)	39(1)
C(12)	2083(4)	5058(1)	6488(2)	65(2)
C(13)	1851(5)	4674(1)	7386(4)	85(2)
C(14)	2426(5)	4770(1)	8810(3)	76(2)
C(15)	3234(4)	5249(1)	9335(2)	66(2)
C(16)	3467(4)	5633(1)	8437(3)	52(1)
C(11')	2745(4)	5499(1)	6824(4)	69(2)
C(12')	1571(4)	5147(2)	6133(4)	73(2)
C(13')	1129(4)	4749(2)	6870(5)	87(2)
C(14')	1861(5)	4703(2)	8299(5)	90(2)
C(15')	3035(5)	5055(2)	8991(4)	91(2)
C(16')	3477(4)	5453(2)	8253(4)	80(2)
C(21)	5558(2)	7491(1)	4360(2)	33(1)
C(22)	6714(2)	7452(1)	5650(2)	41(1)
C(23)	7849(3)	7834(1)	6036(2)	48(1)
C(24)	7851(3)	8264(1)	5153(3)	50(1)
C(25)	6713(3)	8306(1)	3880(3)	53(1)
C(26)	5576(3)	7924(1)	3487(2)	44(1)
C(31)	-922(2)	8880(1)	2166(2)	41(1)
C(32)	-629(3)	9268(1)	3230(3)	55(1)
C(33)	-1588(4)	9703(1)	3115(4)	69(1)
C(34)	-2854(4)	9762(1)	1958(4)	71(1)
C(35)	-3166(3)	9383(1)	904(3)	64(1)
C(36)	-2201(3)	8945(1)	986(3)	51(1)

Table 3

Selected bond lengths [Å] and angles [°] for Compound **6**.

O(1)-C(5)	1.220(3)	N(2)-C(3)-C(4)	112.3(2)
N(1)-C(5)	1.362(3)	C(21)-C(3)-C(4)	126.7(2)
N(1)-N(6)	1.377(2)	N(3)-C(4)-C(3)	118.6(2)
N(1)-N(2)	1.410(2)	N(3)-C(4)-C(5)	112.7(2)
N(2)-C(3)	1.289(2)	C(3)-C(4)-C(5)	100.4(2)
N(3)-C(6)	1.391(3)	N(3)-C(4)-C(2)	109.7(2)
N(3)-C(4)	1.438(3)	C(3)-C(4)-C(2)	107.9(2)
N(4)-C(8)	1.355(3)	C(5)-C(4)-C(2)	106.5(2)
N(4)-N(5)	1.367(3)	O(1)-C(5)-N(1)	127.5(2)
N(5)-C(6)	1.335(2)	O(1)-C(5)-C(4)	127.1(2)
N(6)-C(9)	1.275(3)	N(1)-C(5)-C(4)	105.3(2)
C(1)-C(7)	1.499(3)	N(5)-C(6)-N(3)	120.8(2)
C(2)-C(4)	1.541(3)	N(5)-C(6)-C(7)	112.5(2)
C(3)-C(21)	1.468(3)	N(3)-C(6)-C(7)	126.6(2)
C(3)-C(4)	1.527(3)	C(8)-C(7)-C(6)	104.8(2)
C(4)-C(5)	1.528(3)	C(8)-C(7)-C(1)	128.7(2)
C(6)-C(7)	1.407(3)	C(6)-C(7)-C(1)	126.4(2)
C(7)-C(8)	1.380(3)	N(4)-C(8)-C(7)	106.3(2)
C(8)-C(31)	1.469(3)	N(4)-C(8)-C(31)	121.2(2)
C(9)-C(11')	1.462(3)	C(7)-C(8)-C(31)	132.5(2)
C(9)-C(11)	1.460(3)	N(6)-C(9)-C(11')	117.2(3)
C(5)-N(1)-N(6)	123.9(2)	N(6)-C(9)-C(11)	125.7(2)
C(5)-N(1)-N(2)	113.7(2)	C(12)-C(11)-C(9)	121.5(2)
N(6)-N(1)-N(2)	122.3(2)	C(16)-C(11)-C(9)	118.4(2)
C(3)-N(2)-N(1)	107.7(2)	C(12')-C(11')-C(9)	122.3(3)
C(6)-N(3)-C(4)	122.9(2)	C(16')-C(11')-C(9)	117.7(3)
C(8)-N(4)-N(5)	113.2(2)	C(26)-C(21)-C(3)	121.2(2)
C(6)-N(5)-N(4)	103.3(2)	C(22)-C(21)-C(3)	120.4(2)
C(9)-N(6)-N(1)	116.9(2)	C(36)-C(31)-C(8)	121.5(2)
N(2)-C(3)-C(21)	120.6(2)	C(32)-C(31)-C(8)	120.2(2)

hydrazine hydrate, 115°) finally rearranges to the corresponding pyrazoles **4b** or **3**.

In conclusion, this and our previous results [1,2] show the interest of isoxazol-5-yl hydrazines rearrangement for the access to heterocyclic systems.

EXPERIMENTAL

Melting points were measured on a Kofler apparatus and are uncorrected. The ir spectra were obtained for potassium bromide disks with a Perkin-Elmer 782 spectrometer. The ^{1}H and ^{13}C nmr spectra were recorded for solutions in dimethyl-d_6 sulfoxide using a Bruker AC 200 instrument operating at 200.13 MHz for ^{1}H nmr and at 50.33 MHz for ^{13}C nmr. Chemical shifts are given in ppm relative to internal tetramethylsilane. Assignment of the ^{13}C spectra were made with the aid of DEPT and HETCOR experiments. Electron impact mass spectra (70 eV) were recorded on a VG 70 250S instrument. Merck Kieselgel (230-400 mesh ASTM) was employed for analytical tlc and column chromatography.

Rearrangement of 4-Methyl-3-phenylisoxazol-5-yl Hydrazine **1** in Hydrazine Hydrate.

Compound **1** (50 g, 0.26 mole) and 98% hydrazine hydrate (250 ml) were kept with stirring at 115° for 3.5 hours. The solution was evaporated *in vacuo*, the oily residue was treated with 2*N* sodium hydroxide (200 ml) and the resulting mixture was cooled in the refrigerator overnight. The solid material was filtered, washed with water and crystallised from ethanol to give 1-amino-4-methyl-4-(4-methyl-5-phenyl-1*H*-pyrazol-3-ylamino)-3-phenyl-4,5-dihydro-1*H*-pyrazol-5-one (**3**, 2.5 g, 5.3%) as a white solid, mp 242° dec; ir: ν 3375, 3345, 3300, 3190 (NH, NH_2), 1700 (CO), 1525, 1510 cm^{-1}; ^{1}H nmr: δ 1.56 (3H, s, 4-Me pyrazolone), 2.08 (3 H, s, 4-Me pyrazole), 5.35 (2H, exchangeable br s, NH_2), 6.16 (1H, exchangeable br s, NH), 7.35-7.43 and 7.98-8.03 (10H, m, 2 C_6H_5), 11.67 (1H, exchangeable br s, NH); ^{13}C nmr: δ 8.3 (Me pyrazole), 23.9 (Me pyrazolone), 62.3 (C_4 pyrazolone), 97.3 (C_4 pyrazole), 124.2-131.4 (2 C_6H_5), 139.5 (C_3 pyrazole), 152.9 (C_5 pyrazole), 155.8 (C_3 pyrazolone), 175.4 (CO); ms: (m/z %) 360 (M^+, 65), 345 (11), 332 (14), 316 (10), 303 (68), 288 (49), 273 (12), 215 (34), 198 (22), 184 (18), 173 (100), 157 (13), 155 (10), 144 (12), 132 (13), 130 (26), 115 (60), 104 (39), 103 (24), 96 (15), 91 (19), 89 (11), 77 (41).

Anal. Calcd for $C_{20}H_{20}N_6O$: C, 66.6; H, 5.6; N, 23.3. Found: C, 66.7; H, 5.7; N, 23.1%.

The mother liquors of this compound were evaporated and column chromatographed with ether/methanol 95:5 (v/v) to give, in order of decreasing mobility, the following compounds which were identified on the basis of the spectral properties:

3-phenyl-4-methylpyrazole (**4a**, 6%) [6], 4-amino-4-methyl-3-phenyl-2-pyrazolin-5-one (**5**, 3%) [1], 5(3)-amino-4-methyl-3(5)-phenylpyrazole (**4b**, 10%) [7]; ms: (m/z %) 173 (M^+, 100), 155 (13), 144 (12), 130 (23), 115 (64), 104 (24), 103 (19), 96 (35), 91 (16), 89 (17), 77 (80).

Acidification (*p*H 4) of the alkaline solution gave 1-amino-4-methyl-3-phenyl-2-pyrazolin-5-one (**2**, 20 g, 40%) [1], contaminated (tlc) with a small amount of the corresponding 4-methyl-3-phenyl-2-pyrazolin-5-one.

4-Methyl-4-(4-methyl-5-phenyl-1*H*-pyrazol-3-ylamino)-3-phenyl-1-[(*E*)-1-phenyl-methylideneamino]-4,5-dihydro-1*H*-pyrazol-5-one (**6**).

Condensation of compound **3** (1 mmole) with benzaldehyde (2 mmoles) in methanol (5 ml) gave compound **6** in quantitative yield as white crystals from ethanol, mp 248-249° dec; ir: ν 3380, 3320 (2 NH), 1720 (CO), 1530, 1500, 1460, 1445 cm^{-1}; ^1H nmr: δ 1.72 (3H, s, 4-Me pyrazolone), 2.12 (3 H, s, 4-Me pyrazole), 6.53 (1H, exchangeable br s, NH), 7.29-7.55, 7.85-7.92 and 8.18-8.23 (15H, m, 3 C_6H_5), 8.87 (1H, s, CH), 11.74 (1H, exchangeable br s, NH); ^{13}C nmr: δ 8.0 (Me pyrazole), 23.5 (Me pyrazolone), 63.3 (C_4 pyrazolone), 97.0 (C_4 pyrazole), 126.3-134.0 (3 C_6H_5), 139.4 (C_3 pyrazole), 143.7 (*CH*-Ph), 152.7 (C_5 pyrazole), 159.1 (C_3 pyrazolone), 172.1 (CO).

Anal. Calcd for $C_{27}H_{24}N_6O$: C, 72.2; H, 5.4; N, 18.7. Found: C, 72.0; H, 5.4; N, 18.7.

X-ray Crystal Structure Determination of **6**.

Crystals of compounds **6** suitable for X-ray investigation were obtained by slow evaporation of an ethanolic solution. The cell parameters and intensities were measured on a Siemens P4 diffractometer. The intensities were corrected for Lorentz and polarizations, no absorption correction was applied. The Structure was solved using SHELX86 programs [8] and refined against all F^2 data using SHELXTL System [9]. During the refinement of the non-hydrogen atoms with anisotropic thermal parameters, the hydrogen atoms of the methyl groups were located on the basis of idealised geometry and refined isotropically in the riding mode, the position of the remaining hydrogen atoms were refined isotropically with a common displacement parameter free to refine. The phenyl group of the benzal moiety, disordered between two positions, was refined as a rigid body with a site occupation factor fixed at 0.5 and riding hydrogen atoms located geometrically.

Crystal data and further refinement data are reported in the Table 1. Atomic parameters are shown in Table 2 and the bond lengths and angles are reported in Table 3.

Acknowledgements.

The availability of the Mass Spectrometer and of the X-Ray Diffractometer in the "Centro di Analisi e Determinazioni Strutturali" of the University of Siena is gratefully acknowledged. Work supported by the "Ministero dell'Università e della Ricerca Scientifica e Tecnologica" (MURST).

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