Synthesis of new *N*-acylantipyrylureas and the crystal structure of *N*-benzoyl-*N'*-[4-(2,3-dimethyl-1-phenylpyrazol-5-one)]urea

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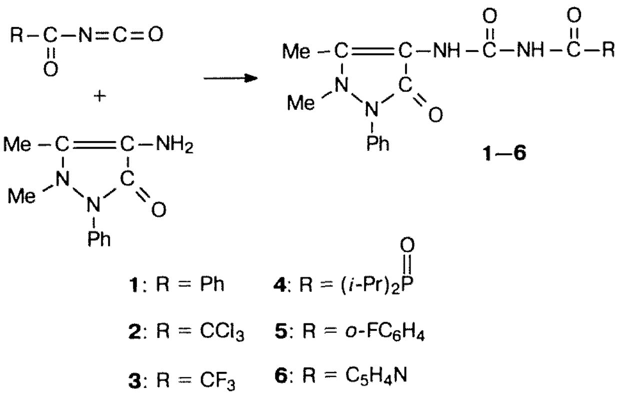
New derivatives of acylheterylureas were synthesized by reactions of acylisocyanates with 4-amino-2,3-dimethyl-1-phenylpyrazol-5-one. The structures of the compounds obtained have been established by IR and ^{1}H NMR spectroscopy. *N*-Benzoyl-*N'*-[4-(1-phenyl-2,3-dimethylpyrazol-5-one)]urea has been studied by X-ray structural analysis. It was found that the molecule adopts an *anti-syn* conformation stabilized by an intramolecular hydrogen bond. In the crystal, molecules are linked in centrosymmetric dimers *via* intermolecular hydrogen bonds.

Key words: *N*-benzoyl-*N'*-[4-(2,3-dimethyl-1-phenylpyrazol-5-one)]urea, X-ray structural study, hydrogen bonds, acylisocyanates, 2,3-dimethyl-1-phenylpyrazol-5-one, biological activity.

It is known[1] that in the crystalline state, many substituted ureas used in medicine and agriculture have a *syn-anti* conformation stabilized by an intramolecular hydrogen bond. Apparently, this factor is essential for participation in biochemical cell processes. It was interesting to study the crystal structures of new antipyrylureas containing at least two biologically active fragments (pyrazoline[2] and urea), which we have synthesized, and to test their biological activities.

Scheme 1



1—6

1: R = Ph

2: R = CCl_3

3: R = CF_3

4: R = $(i\text{-}Pr)_2P(O)$

5: R = $o\text{-}FC_6H_4$

6: R = C_5H_4N

N-Acyl-*N'*-[4-(2,3-dimethyl-1-phenylpyrazol-5-one)]ureas were obtained by reactions of acylisocyanates with 4-amino-2,3-dimethyl-1-phenylpyrazol-5-one (Scheme 1).

The structures of **1—6** have been established from the data of the IR and ^{1}H NMR spectra of the compounds; the structure of compound **1** has also been studied by X-ray structural analysis.

The IR spectra recorded from Nujol mulls showed the ν(C=O) and ν(NH) vibration bands in the regions 1650—1680 cm^{-1} and 3110—3300 cm^{-1}, respectively, that are typical of substituted acylureas.[3] Similarly to the data reported previously,[4] the ^{1}H NMR spectra of compounds **1—5** in CH_2Cl_2 solutions showed two single-proton singlets in the regions 10—11 and 9—10 p.p.m. that were assigned to amide groups. Physical and spectral characteristics of the compounds obtained are given in Tables 1 and 2.

With the aim of establishing the structure and the favorable conformation in the solid state, we carried out X-ray structural study of *N*-benzoyl-*N'*-[4-(2,3-dimethyl-1-phenylpyrazol-5-one)]urea **1**.

The structure of one crystallographically independent molecule is shown in Fig. 1 (the conformations of independent molecules **1A** and **1B** are nearly the same). Atomic coordinates of nonhydrogen atoms in the structure are given in Table 3; the principal geometric parameters are listed in Table 4.

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Table 1. Physicochemical characteristics of compounds synthesized

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula
1	67	199—200	65.00 65.14	5.26 5.14	15.84 16.00	$C_{19}H_{18}N_4O_3$
2	65	207—208	42.80 42.91	3.21 3.32	14.15 14.30	$C_{14}H_{13}Cl_3N_4O_3$
3	42	102—103	48.95 49.12	4.03 3.80	15.68 16.37	$C_{14}H_{13}F_3N_4O_3$
4	28	156—157	52.60 52.68	6.63 6.58	13.00 13.60	$C_{18}H_{27}N_4O_5P$
5	26	170—171	61.40 61.95	4.85 4.61	15.62 15.21	$C_{19}H_{17}FN_4O_3$
6	53	186—187	61.83 61.53	4.62 4.84	20.21 19.94	$C_{18}H_{17}N_5O_3$

Table 2. Spectral characteristics of compounds **1—6**

Compound	IR, ν/cm^{-1} C=O	N—H	^{1}H NMR, δ
1	1610,1650	3230,3420	2.55 (s, 3 H, Me); 7.8 (m, 5H, Ph), 9.10 (s, 1 H, NH); 10.1 (s, 1 H, NH)
2	1620,1690	3200,3400	
3	1620,1750	3120,3420	1.30 (t, 12 H, Pr^i); 2.40 (s, 3 H, Me); 4.90 (m, 2 H); 7.8 (m, 5 H); 10.40 (1 H, NH); 10.50 (s, 1 H, NH)
4	1610,1700	3280,3550	
5	1610,1690	3210,3450	
6	1600,1650	3150,3420	

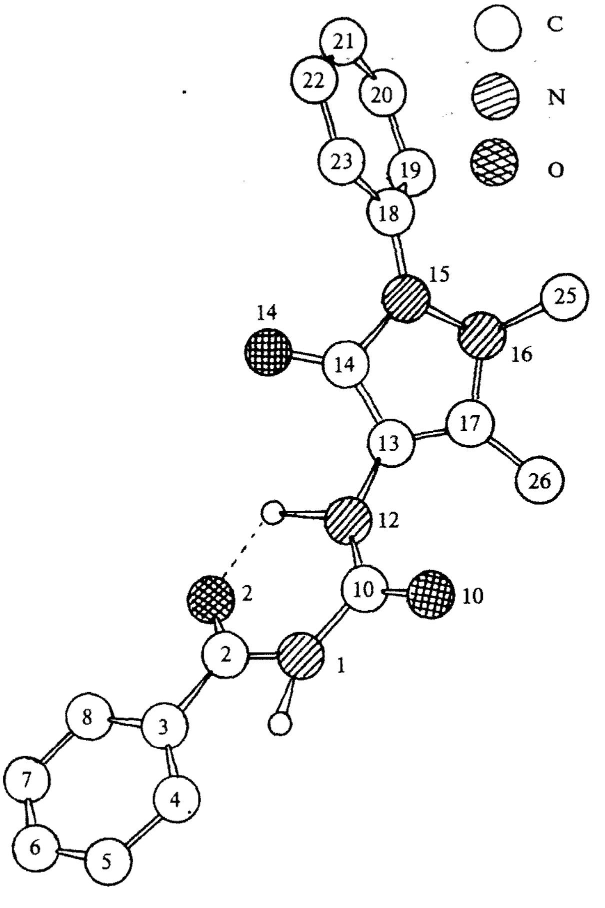

Fig. 1. Geometry of molecule **1A** in the crystal. Hydrogen atoms are not shown.

The urea fragment of molecule **1** adopts a planar *syn-anti* conformation similar to that observed in the structure of *N*-monochloroacetyl-*N'*-tolylsulfonylurea.[5] It is possible that the conformation of molecule **1** observed is stabilized by an intramolecular N(12)—H...O(2) hydrogen bond (see Fig. 1) with the following parameters: N(12)—H 0.99 Å, N(12)...O(2) 2.615(7) Å, H...O(2) 1.86 Å, the N(12)—H...O(2) angle 130° for molecule **1A** and N(12)—H 1.23 Å, N(12)...O(2) 2.602(7) Å, H...O(2) 1.50 Å, the N(12)—H...O(2) angle 144° for molecule **1B**.

In molecules **1**, the plane of the C(3)—C(8) benzene ring is nearly coplanar with the plane of the O(2)—C(2)—N(1)—C(10)—N(12) urea fragment (the average value of the dihedral angles between these planes is 12.6°). In the molecules of phenylurea and *N*-methyl-*N'*-phenylurea, the dihedral angles between the corresponding planes are 30° and 27°, respectively.

The diazocyclopentene heterocycle of the molecule is planar; the dihedral angle between this plane and the plane of the central fragment is 58.5°. Apparently, the twist about the N(12)—C(13) bond is caused by steric reasons (the presence of substituents at the C(14) and C(17) atoms of the heterocycle). Because of this, the C(18)—C(23) benzene ring is twisted by 48.8° out of the plane of the heterocycle.

Unfortunately, a low accuracy of determination of geometric parameters of molecule **1** does not allow us to discuss the possible manifestations of conjugation effects in the molecule.

In the crystal, molecules **1** are linked in centrosymmetric dimers *via* intermolecular hydrogen bonds with the following parameters: N(1)...O(10')(−*x*,−*y*,−*z*) 2.901(7) Å, N(1)—H 0.97 Å, H...O(10') 1.96 Å, the N(1)—H...O(10') angle 163° (for molecule **1A**) and N(1)...O(10") (1−*x*, −*y*, 1−*z*) 2.877(7) Å, N(1)—H 1.11 Å, H...O(10") 1.79 Å, the N(1)—H...O(10") angle 166° (for molecule **1B**).

Table 3. Atomic coordinates of nonhydrogen atoms in the structure of **1**, their equivalent isotropic temperature factors $B_{\rm iso}^{\rm eq} = \frac{4}{3}\sum^{3}\sum^{3}(a_i,\ a_j) \cdot B(i,j)$, and isotropic temperature factors of carbon atoms of benzene rings $B_{\rm iso}$

Atom	*x*	*y*	*z*	*B*/Å^2	*x*	*y*	*z*	*B*/Å^2
	Molecule **A**				Molecule **B**			
O(2)	0.3599(8)	0.0612(5)	0.1789(4)	5.8(2)	0.9023(8)	0.0988(4)	0.3321(4)	6.3(2)
O(10)	−0.0665(7)	0.0989(4)	0.0378(4)	5.6(2)	0.4463(8)	0.1105(4)	0.4667(4)	6.3(2)
O(14)	0.2490(7)	0.3479(5)	0.1073(5)	6.2(2)	0.7716(7)	0.3840(5)	0.4022(5)	6.4(2)
N(1)	0.1784(8)	0.0199(5)	0.0844(4)	3.8(2)	0.6956(8)	0.0385(5)	0.4230(5)	4.5(2)
N(12)	0.0809(9)	0.1617(5)	0.1366(5)	4.7(2)	0.6250(9)	0.1954(5)	0.3759(5)	4.6(2)
N(15)	−0.0328(8)	0.4097(5)	0.1274(5)	4.4(2)	0.4882(8)	0.4407(5)	0.3751(5)	4.0(2)
N(16)	−0.1954(8)	0.3702(5)	0.1550(5)	4.7(2)	0.3391(9)	0.4012(5)	0.3473(5)	4.6(2)
C(2)	0.327(1)	0.0085(6)	0.1261(6)	4.4(2)	0.848(1)	0.0332(6)	0.3798(6)	4.8(2)
C(3)	0.456(1)	−0.0692(6)	0.1051(6)	4.1(2)*	0.957(1)	−0.0539(6)	0.3932(6)	4.3(2)*
C(4)	0.433(1)	−0.1331(6)	0.0477(6)	4.5(2)*	0.943(1)	−0.1224(7)	0.4564(6)	4.9(2)*
C(5)	0.568(1)	−0.1991(7)	0.0320(6)	5.1(2)*	1.056(1)	−0.2018(7)	0.4641(6)	5.3(2)*
C(6)	0.719(1)	−0.2009(7)	0.0746(6)	5.9(3)*	1.190(1)	−0.2111(8)	0.4092(7)	7.3(3)*
C(7)	0.742(1)	−0.1391(7)	0.1278(6)	5.5(2)*	1.213(2)	−0.142(1)	0.3472(9)	9.9(4)*
C(8)	0.610(1)	−0.0711(7)	0.1467(6)	5.2(2)*	1.092(1)	−0.0631(8)	0.3364(7)	7.1(3)*
C(10)	0.054(1)	0.0967(6)	0.0835(5)	3.7(2)	0.582(1)	0.1165(7)	0.4244(6)	5.0(3)
C(13)	−0.006(1)	0.2517(6)	0.1339(6)	4.3(2)	0.532(1)	0.2842(6)	0.3744(6)	4.0(2)
C(14)	0.090(1)	0.3368(6)	0.1202(6)	4.2(2)	0.620(1)	0.3692(7)	0.3885(6)	4.8(2)
C(17)	−0.173(1)	0.2724(6)	0.1529(5)	3.7(2)	0.370(1)	0.3032(6)	0.3522(6)	4.5(2)
C(18)	0.004(1)	0.5039(7)	0.1426(6)	4.6(2)*	0.523(1)	0.5385(6)	0.3556(5)	3.8(2)*
C(19)	−0.054(1)	0.5468(7)	0.2123(6)	5.2(2)*	0.472(1)	0.5862(6)	0.2854(6)	4.6(2)*
C(20)	−0.002(1)	0.6386(7)	0.2217(6)	5.8(2)*	0.519(1)	0.6809(7)	0.2686(6)	4.8(2)*
C(21)	0.104(1)	0.6892(8)	0.1680(7)	6.7(3)*	0.607(1)	0.7264(7)	0.3250(6)	5.4(3)*

*Atoms were refined isotropically.

Table 4. Bond lengths (*d*) and bond angles (ω) in molecules **1**

Bond	*d*/Å	
	1A	**1B**
O(2)—C(2)	1.230(8)	1.236(7)
O(10)—C(10)	1.217(7)	1.237(8)
O(14)—C(14)	1.236(7)	1.217(8)
N(1)—C(2)	1.353(8)	1.350(8)
N(1)—C(10)	1.419(8)	1.380(8)
N(12)—C(10)	1.346(8)	1.357(8)
N(12)—C(13)	1.412(8)	1.422(8)
N(15)—N(16)	1.420(6)	1.392(6)
N(15)—C(14)	1.383(8)	1.415(8)
N(15)—C(18)	1.406(8)	1.415(7)
N(16)—C(17)	1.383(8)	1.387(8)
N(16)—C(25)	1.481(8)	1.480(9)
C(2)—C(3)	1.505(9)	1.470(9)
C(13)—C(14)	1.419(8)	1.427(9)
C(17)—C(26)	1.502(9)	1.477(9)

Angle	ω/ged	
	1A	**1B**
C(2)—N(1)—C(10)	128.3(6)	126.6(6)
C(10)—N(12)—C(13)	123.0(6)	124.7(6)
N(16)—N(15)—C(14)	109.3(5)	110.1(5)
N(16)—N(15)—C(18)	119.6(5)	120.1(5)
C(14)—N(15)—C(18)	125.2(6)	123.9(5)
N(15)—N(16)—C(17)	105.6(5)	106.1(5)
N(15)—N(16)—C(25)	115.9(5)	114.9(5)
C(17)—N(16)—C(25)	121.6(6)	120.0(6)
O(2)—C(2)—N(1)	121.7(7)	123.4(7)
O(2)—C(2)—C(3)	120.0(7)	118.9(7)
N(1)—C(2)—C(3)	118.3(7)	117.6(7)
O(10)—C(10)—N(1)	119.7(6)	119.3(7)
O(10)—C(10)—N(12)	125.3(6)	123.4(7)
N(1)—C(10)—N(12)	115.0(6)	117.1(7)
N(12)—C(13)—C(14)	120.3(6)	120.1(6)
N(12)—C(13)—C(17)	128.8(7)	128.0(7)
C(14)—C(13)—C(17)	110.3(6)	111.4(6)
O(14)—C(14)—N(15)	125.1(7)	125.0(7)
O(14)—C(14)—C(13)	130.2(7)	132.2(7)
N(15)—C(14)—C(13)	104.6(6)	102.5(6)
N(16)—C(17)—C(13)	109.5(5)	109.4(6)
N(16)—C(17)—C(26)	119.4(6)	118.0(6)
C(13)—C(17)—C(26)	131.0(7)	132.5(7)

Therefore, in this work, new *N*-antipyryl-*N'*-acylureas were synthesized and one compound was studied by X-ray structural analysis. It was found that the molecule adopts an *anti-syn* conformation stabilized by intramolecular hydrogen bonds to form centrosymmetric dimers.

Preliminary screening of biological activities of the compounds obtained revealed the moderate biological activity toward some bacteria and fungi.

Experimental

The IR spectra were recorded on a Specord M-80 instrument in the region 400—3600 cm^{-1} using Nujol mulls on KBr plates. The ^{1}H NMR spectra were obtained on a Tesla BS-467 instrument (60 MHz). Anhydrous solvents were used for washing and recrystallization.

***N'*-Benzoyl-*N'*-[4-(2,3-dimethyl-1-phenylpyrazol-5-one)]urea 1**. 4-Aminoantipyrine (0.05 mol) was added to a solution of benzoylisocyanate (0.05 mol) in ether with intense stirring using a magnetic stirrer at room temperature under a dry argon atmosphere.

Compound **2—6** were obtained by an analogous procedure (see Tables 1 and 2).

Crystals of **1**, $C_{19}H_{18}N_4O_3$, are triclinic. At 20 °C, a = 7.648(2) Å, b = 14.051(4) Å, c = 16.657(6) Å, α = 85.35(2)°, β = 87.86(2)°, γ = 88.52(2)°, d_{calc} = 1.31 g cm^{-3}, Z = 4, space group $P\bar{1}$ (two independent molecules **A** and **B**). The unit-cell parameters and intensities of 1697 independent reflections with $F^2 > 3\sigma$ were measured on a four-circle automated Enraf-Nonius CAD-4 diffractometer with the K geometry (Mo-Kα radiation, graphite monochromator, $\omega/(5/3\ \theta)$ scanning technique, $\theta \leq 25°$). The structure was solved by the direct method using the MULTAN program and refined first with isotropic temperature factors and then with anisotropic (O, N, and carbon atoms of the central part of the molecule) temperature factors. Hydrogen atoms were revealed from the difference electron density series; their contributions to structure amplitudes were taken into account in the final cycles of the refinement, in which hydrogen atoms were included with fixed positional and isotropic temperature parameters (B_{iso} = 4.5 Å^2). The final value of the R factors were as follows: R = 0.072, R_w = 0.101.

All calculation were carried out on a PDP 11/23 computer using the SDP program package.

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