Synthesis and Structural Analysis of 5-Cyanodihydropyrazolo[3,4-*b*]pyridines

Jairo Quiroga*, Silvia Cruz, Braulio Insuasty and Rodrigo Abonia

Grupo de Investigación de Compuestos Heterocíclicos. Departamento de Química, Universidad del Valle, A. A. 25360, Cali – Colombia

Justo Cobo, Adolfo Sánchez and Manuel Nogueras*

Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain

John N. Low

Department of Applied Physics and Electronic & Mechanical Engineering, University of Dundee, Dundee DD1 4HN, Scotland

Received April 17, 2000

Several new 3-aryl-5-cyanopyrazolo[3,4-*b*]pyridines were easily prepared from 3-amino-5-arylpyrazoles and α-cyanochalcones. Structural analysis using NMR solution studies revealed the 2*H*-tautomers as the preferred tautomer in solution (DMSO-d_6). X-ray diffraction confirmed the 2*H*-tautomers as the unique tautomer species in the crystalline state as well. Geometry optimization of 1*H* and 2*H*-tautomers at semi-empirical levels (AM1, MINDO/3) were performed, indicating that in all cases the 2*H*-tautomers are more stable than the corresponding 1*H*-tautomers.

J. Heterocyclic Chem., **38**, 53 (2001).

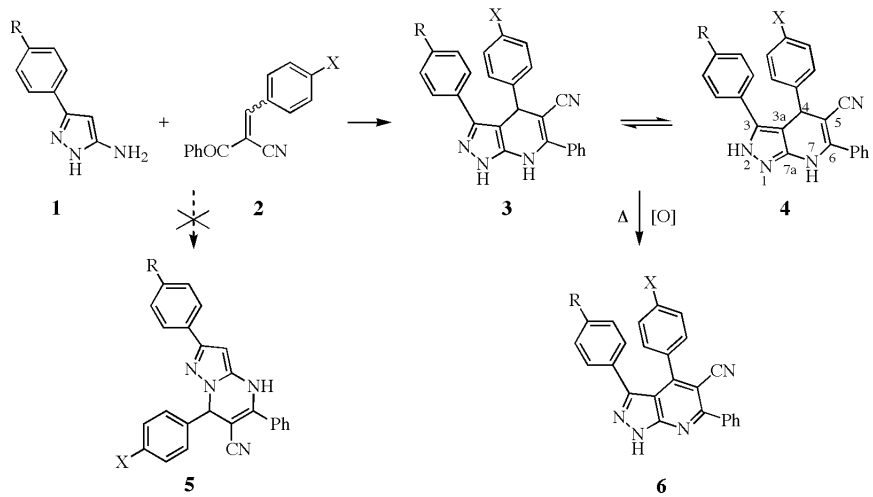
Introduction.

The pyrazolo[3,4-*b*]pyridine system has interesting biological and pharmacological properties [1-4], such as ACTH(Adrenocorticotropic hormone)-releasing factor (CRF(Corticotropin-releasing factor)) antagonist activity. CRF antagonists are believed to be effective in the treatment of a wide variety of stress-related illnesses, such as depression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, haemorrhaged stress, drug and alcohol withdrawal symptoms, drug addition and infertility [5]. Dihydropyrazolo[3,4-*b*]pyridines have also shown vasodilating and anti-hypertension activities and produced prophylactic effects as calcium antagonists in stroke-prone spontaneously hypertensive rats [6], and even been used as dyes [7].

Continuing our research on the reaction of aminopyrazoles with α,β-unsaturated compounds, [8-17] we report, here, the reactions between 3(5)-aminopyrazoles (**1**) and α-cyanochalcones (**2**), which can lead to, in a first instance, either dihydropyrazolo[3,4-*b*]pyridine (**3**/**4**), similar to that previously reported [8,13-14,17], or to dihydropyrazolo[1,5-*a*]pyrimidine **5**, such as the previously reported [9-10,12,16] (see Scheme 1).

A related study has been carried out with similar structures, although the dihydropyrazolo[3,4-*b*]pyridines were prepared in a different way starting from the appropriate 1,4-dihydropyridines and hydrazine. In that investigation the 1*H* tautomer was found to be the preferred, through the use of x-ray and semiempirical calculation [18]. In the present paper, we

Scheme 1



will show that the phenyl residue at the pyrazole moiety may be responsible for observation that dihydropyrazolo[1,5-*a*]-pyrimidines to found exist as the 2*H* tautomer.

Results and Discussion.

Refluxing 3(5)-amino-5(3)-arylpyrazoles **1** with cyanochalcones **2** in ethanol allowed the isolation of 3,4-diaryl-5-cyano-6-phenylpyrazolo[3,4-*b*]pyridines **3**/**4** by simple filtration in good to excellent yields (56-83%). The formation of compounds with structure such as **3**/**4** was confirmed by spectroscopic analysis. Possible structures such as pyrazolo[1,5-*a*]pyrimidines **5** for the isolated products were excluded based on NMR examination, because of the absence of signals for H-3 (H-4 in precursors **1**). The tautomerism and properties of the 5-cyanodihydropyrazolo[3,4-*b*]pyridines **3** or **4** have been determined.

IR spectra of compounds **3**/**4** showed two typical bands of the elongation vibrations of secondary NH groups around 3240-3270 cm^{-1} and a band typical of CN groups around 2200-2215 cm^{-1}.

Table 1
^{1}H-NMR Data of Pyrazolo[3,4-*b*]pyridines **3**/**4a-k.**

			δ ppm											
							3-Aryl			4-Aryl			6-Phenyl	
Entry	R	X	$H_{1(2)}$	H_4	H_7	H_o	H_m	R_p	H_o	H_m	X_p	H_o	H_m	H_p
a	H	Cl	12.70	5.39	10.16	7.54	7.57	7.56	7.33	7.25	----	7.52	7.48	7.50
b	CH_3	Cl	12.69	5.35	10.13	7.38	7.17	2.26 [a]	7.30	7.24	----	7.52	7.51	7.54
c	OCH_3	Cl	12.61	5.32	10.12	7.43	6.91	3.74 [a]	7.31	7.21	----	7.50	7.48	7.53
d	Cl	Cl	12.83	5.39	10.19	7.41	7.05	----	7.31	7.24	----	7.61	7.51	7.91
e	Br	Cl	12.86	5.37	10.27	7.49	7.00	----	7.39	7.32	----	7.61	7.53	7.87
f	NO_2	Cl	13.15	5.50	10.29	8.19	7.82	----	7.32	7.28	----	7.50	7.48	7.56
g	H	H	12.71	5.29	10.11	7.53	7.49	7.52	7.23	7.22	7.16	7.28	7.28	7.32
h	H	CH_3	12.71	5.24	10.08	7.50	7.52	7.54	7.07	7.05	2.20 [a]	7.47	7.26	7.34
i	H	OCH_3	12.70	5.24	10.07	7.54	7.33	7.50	7.13	6.80	3.36 [a]	7.49	7.27	7.46
j	H	Br	12.76	5.36	10.17	7.51	7.49	7.15	7.15	7.43	-----	7.56	7.27	7.35
k	H	NO_2	12.83	5.60	10.29	7.55	7.52	7.50	7.55	8.12	----	7.57	7.26	7.34

[a] Integrate for 3H and correspond to CH_3 groups

Table 2
^{13}C-NMR Data of Pyrazolo[3,4-b]pyridines **3**/**4a-k**

Carbon						δ (ppm)					
Atom	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**
C-3 [a]	137.8	137.4	137.8	137.6	137.6	134.7	137.5	137.4	137.4	137.6	138.0
C-3a [a]	99.6	99.0	100.4	100.7	98.3	101.3	99.9	100.0	100.1	99.3	98.8
C-4 [b]	39.9	39.4	39.4	39.7	39.7	39.3	39.8	39.7	39.9	39.4	39.7
C-5 [a]	80.1	80.0	79.9	80.0	80.9	80.1	80.3	80.6	80.8	79.8	79.0
C-6 [a]	150.2	150.4	150.4	159.8	159.9	150.4	150.2	149.3	149.8	150.4	150.9
C-7a [a]	147.7	147.5	150.6	152.2	154.1	148.0	147.7	147.7	147.7	147.5	147.4
CN [a]	121.5	121.5	121.5	121.4	121.4	121.3	121.6	121.7	121.7	121.5	121.2
3-Aryl											
C_i [a]	130.1	128.4	123.2	130.0	129.4	135.6	128.9	129.3	128.9	129.6	128.7
C_o [b]	126.3	126.1	129.2	130.4	128.8	127.1	128.4	128.5	127.8	128.5	128.4
C_m [b]	128.0	129.2	113.9	130.2	131.4	123.8	126.2	127.8	126.1	127.7	128.3
C_p	128.4 [b]	137.7 [a]	158.9 [a]	132,5 [a]	121,4 [a]	146.3 [a]	129.9 [b]	128.4 [b]	128.4 [b]	128.4 [b]	128.1 [b]
R		20.6 [b]	55.1 [b]								
4-Aryl											
C_i [a]	144.5	144.5	144.5	144.2	144.7	144.0	145.6	142.8	137.9	144.8	152.4
C_o [b]	129.3	129.1	129.9	128.3	129.2	129.3	126.5	127.2	128.4	119.6	128.6
C_m [b]	128.3	128.3	129.2	127.5	128.3	128.4	128.4	128.9	113.6	128.7	123.7
C_p	131.2 [a]	131.1 [a]	131.1 [a]	131.1 [a]	131.1 [a]	131.3 [a]	127.3 [b]	135.5 [a]	157.7 [a]	121.8 [a]	146.1 [a]
X								20.5 [b]	54.8 [b]		
6-Phenyl											
C_i [a]	134.1	134.0	134.0	137.6	137.6	133.9	134.1	134.1	134.2	134.0	133.8
C_o [b]	128.5	129.2	128.3	128.4	128.7	128.4	128.3	128.3	128.5	128.3	128.4
C_m [b]	128.6	128.4	127.9	128.0	128.1	128.4	127.9	126.1	128.3	126.2	126.2
C_p [b]	130.1	130.0	127.6	130.0	130.4	130.1	128.3	129.9	129.9	130.0	130.1

[a]Signal disappeared after DEPT-135 experiment. [b]Signal maintained after DEPT-135 experiment

^{1}H-NMR spectra of compounds **3/4a-k** show three singlets in addition to signals corresponding to aromatic protons found between 7.07 and 8.12 ppm. Those signals correspond to protons 5-H (between 5.24 and 5.60 ppm) and two deuterium exchangeable protons 1(2)-NH and 7-NH (around 12.8 and 10.1 ppm). ^{1}H and ^{13}C-NMR spectra are displayed in Tables 1 and 2. Multiplicity of carbon atoms was determined by ^{13}C-nmr (DEPT-135 experiment) spectroscopy, and is consistent with the proposed structures **3**/**4**.

In the reaction to prepare compound 3/4d, the corresponding oxidised product 6d was also isolated along with the former. Compound 6d was isolated and fully characterised after heating of the reaction mixture for a long period of time.

NMR Solution Study.

Complete assignment of the carbon atoms using HSQC and HMBC experiments permitted the determination of the preferred tautomer as 2*H* **4**. Table 3 shows the long range proton-carbon couplings found in the HMBC spectra of compound **4g-k** for H-2 and H-7 protons.

Table 3

HMBC Spectra Data of Compounds **4g-k**.
Correlations Found for Protons H-2 and H-7

	H-2		H-7	
Compound	^2J	^3J	^2J	^3J
4g	C-3	C-3a, C-7a	C-6	C-3a, C-5, C_i Phenyl
4h	C-3	C-3a, C-7a		C-3a, C-5
4i	C-3	C-3a, C-7a	C-6	C-3a, C-5, C_i Phenyl
4j	C-3	C-3a, C-7a		C-3a, C-5
4k	C-3	C-3a, C-7a		C-3a, C-5, C_i Phenyl

After the complete assignment, ^{13}C-nmr results were correlated with those of corresponding 3-amino-5-aryl-1-methyl- and 5-amino-3-aryl-1-methyl-pyrazoles **7** and **8** respectively [19], and with 2*H*-dihydropyrazolo[3,4-*b*]-pyridin-6-ones **9** [17] in order to establish a relation between their ^{13}C chemical shifts and the tautomerism.

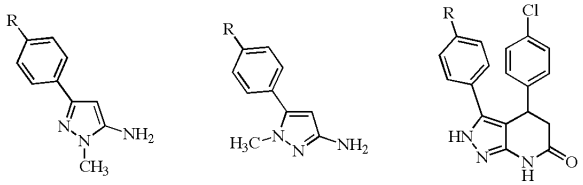
Comparison of ^{13}C chemical shifts of the 3-aryl groups in compounds **3/4a-f** with those of the *N*-methyl derivatives **7** and **8** (see Figure 1) [20] resulted in the following two correlation equations:

$$\delta(\mathbf{3/4}) = 10.64 + 0.918\ \delta(\mathbf{7}),\ n = 24,\ r^2 = 0.918 \quad (1)$$

$$\delta(\mathbf{3/4}) = 2.40 + 0.997\ \delta(\mathbf{8}),\ n = 24,\ r^2 = 0.991 \quad (2)$$

In the comparison of the ^{13}C chemical shifts of the 3-aryl groups in compounds **3/4a-f** with those of the 2*H*-dihydropyrazolo[3,4-*b*]pyridin-6-ones **9** the correlation Equation 3 shown below resulted:

$$\delta(3/4) = 2.40 + 0.984\ \delta(9),\ n = 24,\ r^2 = 0.990 \quad (3)$$



7 **8** **9**

Figure 1

Table 4

Selected Intra and Inter-molecular Parameter (Å, °). See Figure 2 for Atom Labelling Scheme

	4b (mol. 1)	**4b** (mol. 2)	**4f** (mol. 1)	**4f** (mol. 2)	**4i**	**6d**
N1-N2	1.355(3)	1.356(3)	1.360(7)	1.363(7)	1.363(2)	1.367(3)
N2-C3	1.355(3)	1.353(3)	1.371(8)	1.359(8)	1.357(2)	1.328(3)
C3-C3a	1.399(4)	1.382(4)	1.389(8)	1.388(9)	1.394(2)	1.435(4)
C3a-C4	1.508(4)	1.505(4)	1.509(8)	1.510(8)	1.508(2)	1.401(4)
C4-C5	1.530(4)	1.539(4)	1.533(8)	1.522(8)	1.535(2)	1.400(4)
C5-C6	1.358(4)	1.365(4)	1.357(9)	1.369(9)	1.362(2)	1.427(4)
C6-N7	1.375(3)	1.370(3)	1.369(8)	1.362(8)	1.369(2)	1.335(3)
N7-C7a	1.384(4)	1.387(3)	1.389(8)	1.381(8)	1.388(2)	1.347(4)
C7a-N1	1.324(3)	1.332(3)	1.323(8)	1.331(8)	1.332(2)	1.348(3)
C7a-N1-N2	103.1(2)	102.9(2)	103.7(5)	103.1(5)	102.37(13)	111.9(2)
N1-N2-C3	113.6(2)	113.2(2)	112.3(5)	113.1(5)	113.78(14)	106.5(2)
N2-C3-C3a	105.7(2)	106.2(2)	106.6(5)	106.5(5)	105.82(15)	110.2(3)
C7a-N7-C6	119.1(2)	118.9(2)	118.0(5)	119.3(5)	118.52(14)	114.7(3)
N7-C6-C5	120.8(3)	121.3(2)	122.1(6)	120.1(6)	121.14(16)	121.7(3)
C6-C5-C4	125.8(3)	125.4(2)	125.8(5)	126.5(6)	125.54(15)	122.5(3)
C5-C4-C3a	108.4(2)	108.3(2)	107.5(5)	107.3(5)	108.29(13)	115.7(3)
C4-C3a-C7a	122.2(3)	122.5(2)	122.8(5)	121.8(5)	121.82(15)	117.1(3)
C3a-C7a-N7	123.3(3)	123.7(2)	123.4(5)	123.3(5)	124.04(15)	128.1(3)
N1-C7a-N7	122.8(2)	122.8(2)	122.7(5)	123.1(6)	121.81(15)	125.0(3)
C4-C3a-C7a-N7	-2.8(4)	-1.0(4)	-3.0(9)	0.3(9)	-3.0(3)	1.1(5)
N1-N2-C3-C3a	0.4(3)	-0.8(3)	-1.6(7)	-0.8(7)	0.01(19)	0.9(3)

Table 4 (continued)

	4b (mol. 1)	**4b** (mol. 2)	**4f** (mol. 1)	**4f** (mol. 2)	**4i**	**6d**
N7-C6-C5-C4	-3.7(5)	-1.5(4)	7.1(10)	9.4(10)	-10.4(3)	-2.3(4)
C6-C5-C4-C(Ar2)	-127.2(3)	-123.9(3)	119.2(7)	110.1(7)	118.95(18)	-178.9(3)
C4-C5-C6-C(Ar3)	175.5(3)	-179.2(3)	-175.3(6)	-172.1(6)	167.99(15)	177.2(3)
N1-N2-C3-C(Ar1)	178.6(2)	176.9(2)	178.2(5)	179.4(5)	178.48(15)	-179.6(3)

Compound	D-H...A	D-H	D...A	H...A	D-H...A
4b	N2-H2 (Mol. 1)...N1 (Mol. 2) (-x+1, -y+1, -z)	0.88	2.801(4)	2.05	142
	N2-H2 (Mol. 2)...O1 (DMF) (-x+1, -y+1, -z+1)	0.88	2.775(3)	1.92	163
	N7-H7 (Mol. 2)...N1 (Mol. 1) (-x+1, -y+1, -z)	0.88	2.890(3)	2.07	155
4f	N2-H2 (Mol. 1)...O (EtOH-A)	0.88	2.837(7)	2.10	144
	N2-H2 (Mol. 2)...O (EtOH-B)	0.88	2.833(7)	2.10	139
	O-H (EtOH-B)...N ≡C(Mol. 2) (-x+1, -y, -z)	0.84	2.868(8)	2.03	174
	O-H (EtOH-A)...N ≡C(**M**ol. 1) (-x+1, -y+1, -z+1)	0.84	2.829(8)	1.99	176
4i	N2-H2...N ≡C ($x+^1/_2$, $y-^1/_2$, z)	0.88	3.016(2)	2.18	159
	N7-H7...N1 (-x, y , ?-z)	0.88	3.065(2)	2.33	142
6d	N1-H1...N7 (-x+2, -y+2, z)	0.88	2.936(3)	2.07	167

Much better correlation coefficients and slopes resulted from the use of Equations 2 and 3 which relates to the 2*H*-tautomers **8** and **9** than from the use of Equation 1 which relates to 1*H*-tautomer **7**, thus showing that all bicycles **3/4** exist as 2*H*-tautomers **4** in DMSO solution.

Additional information was given by the NOESY experiment carried out on compounds **4g** and **4h.** The NOE interaction between signals around 12.7 (corresponding to N(2)-H according to HMBC) and *ortho*-H of 3-aryl residues at 7.53 ppm (**4g**) and 7.50 ppm (**4h**) confirms the 2*H*-tautomers as being predominant [21-22].

X-ray Crystallographic Study.

Some of compounds of **3**/**4** were crystalline, and X-ray diffraction studies were carried out on compound **3/4b**, **f** and **i**, which show similar bonds lengths and angles (the average values for these parameters are listed in Table 4). The oxidised derivative **6d** from **3**/**4d** also provided a crystalline product, and its structural study is reported.

As can be seen in Figure 1 the crystal of compounds **4b** and **4f** contain solvent molecules (one of DMF for **4b** and two of EtOH for **4f**) in their asymmetric units. Similar ring conformations for the orientation of the phenyl group at C-4 to that previously reported [18] was found.

The pyrazole rings are essentially planar (ring puckering analysis [23,24] afforded τ_{max} of 1.2°) showing aromatic character, although the bond C7a-N1 has a larger double bond contribution than does C3-N2. This, along with the observation that the hydrogen atoms in every case were located unequivocally on difference maps at N2 atoms, shows unambiguously that the 2*H*-tautomers **4** are preferred in the solid state, in agreement with solution studies.

The dihydropyridine rings in most of these compounds are nearly planar showing a τ of approximately 4° except in the case of compound **4f** where molecule 2 in the asymmetric unit presents a skew boat conformation with the following puckering co-ordinates [23,24]: amplitude Q = 0.131 (7), angles θ = 74.1 (31)° and ϕ = 158 (3)°. The pyrazole and pyridine rings are nearly coplanar with each other, having dihedral angles between 1.6 and 6.1°, and the phenyl groups attached at C-4 are nearly perpendicular to the pyridine rings (dihedral angle from 80.4 to 86.5°).

As far as the remaining aryl residues are concerned: those at C-6 are rotated relative to the pyridine rings between 40.55 and 58.8°. In contrast, those attached to C-3 are slightly different in each compound, in **4b** the pyrazole rings are rotated with a mean dihedral angle of 26°, in **4f** around 19°, and finally **4i** presents coplanarity between that aryl-3 and the pyrazole ring (dihedral angle of 4.8°).

Hydrogen bond data for all compounds are listed in Table 4, and also confirm the identity of the 2*H*-tautomer.The two molecules of the asymmetric unit in **4b** form a dimeric structure (Figure 2), with the interactions N2-H (Mol. 1)...N1 (Mol. 2) and N7-H (Mol. 2)...N1 (Mol. 1) linking each other.

In compound **6d**, both bond lengths and angles of the pyrazolo[3,4-*b*]pyridine moiety are those expected for an aromatic system, both rings are planar (τ of 0.8 and 1.7° for pyrazole and pyridine rings respectively) with a dihedral angle of 2.5°. The aryl residues are rotated with respect to the main plane with dihedral angles of 43 to 54°. The hydrogen bonding pattern is quite similar to that described for **4b**, in which dimeric units are also formed by interactions N1-H....N7 of different molecules.

Semiempirical Calculation.

Semiempirical calculations have been carried out with MOPAC at AM1 [25-26] and MINDO/3 [27] levels to explain the experimental findings. After optimisation of structures **3** and **4** a comparison of geometrical parameters for **4b,f,i** and **6d** with those from X-ray diffraction was

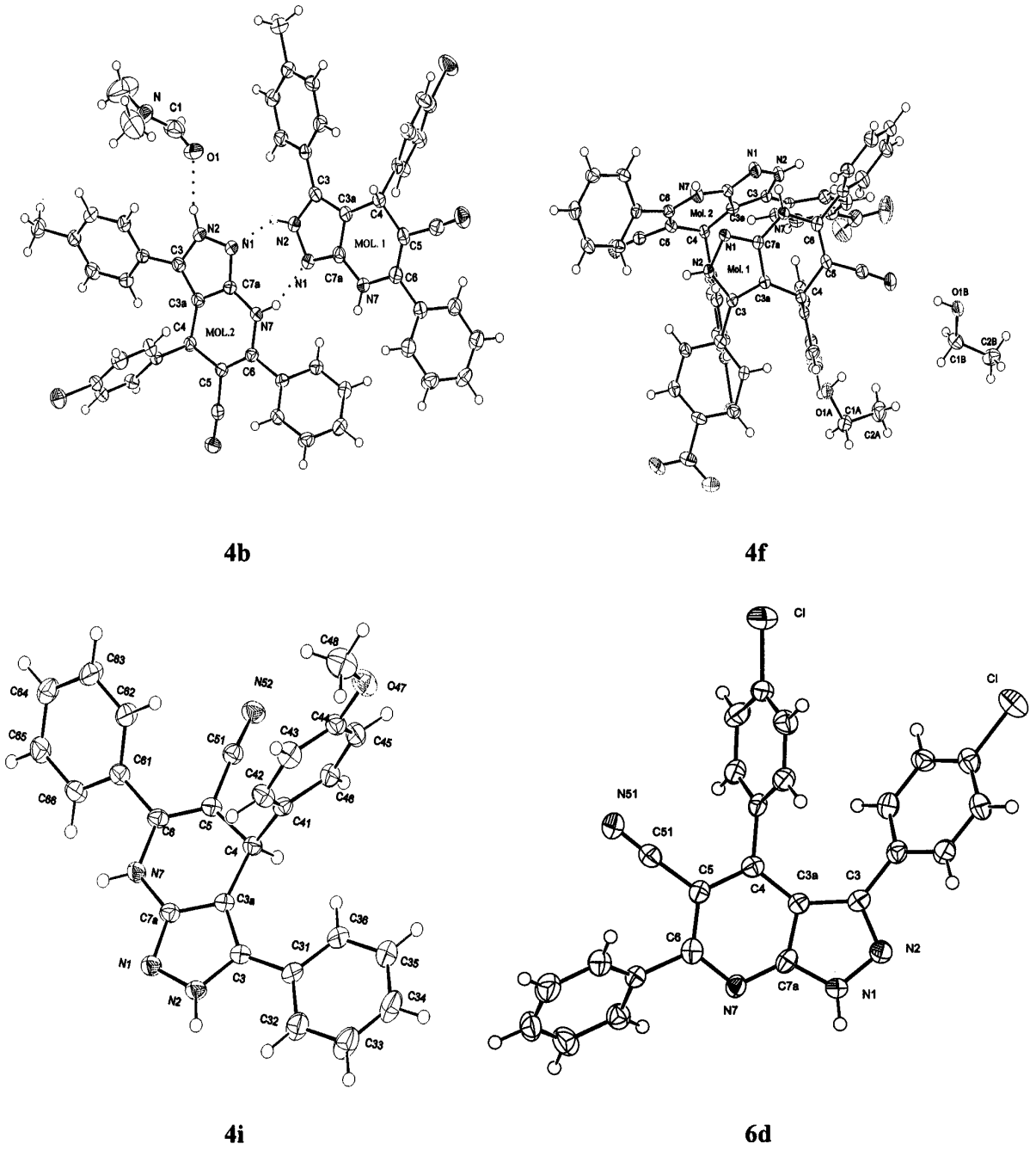


Figure 2. Perspective views of asymmetric units. Displacement ellipsoids are scaled to 30% probability level. Dotted lines represent hydrogen bonds.

carried out to check the method (Table 5). Then, the relative stability of the 1*H*- and 2*H*-tautomers **3** and **4** were examined, and it was established that compounds **4** are slightly more stable than the corresponding compounds **3**. This is shown in Table 6.

Conclusions.

Several 3-aryl-5-cyano-pyrazolo[3,4-*b*]pyridines have been prepared in good to excellent yields by cyclocondensation between 3-aminopyrazoles and cyanochalcones. The tautomerism analysis by solution NMR, crystallographic and theoretical studies showed the 2*H*-tautomer as the predominant form both in solution and in solid states. The presence of the phenyl ring at C-3 and its possible delocalization with pyrazole ring seems to be the main reason for why the 2*H* tautomers are preferred in compounds **4** over that of 1*H* tautomers (found in [18] as the preferred). The finding that the 1*H* tautomer as the preferred in compound **6d**, where the phenyl is

Table 5

Selected Molecular Parameter (Å, °)
Afforded from AM1 Level Calculations

	4b	**4f**	**4i**	**6d**
N1-N2	1.332	1.330	1.331	1.323
N2-C3	1.407	1.408	1.408	1.396
C3-C3a	1.407	1.407	1.406	1.418
C3a-C4	1.478	1.476	1.475	1.415
C4-C5	1.511	1.510	1.511	1.388
C5-C6	1.371	1.370	1.373	1.454
C6-N7	1.405	1.404	1.405	1.325
N7-C7a	1.400	1.399	1.391	1.382
C7a-N1	1.378	1.377	1.376	1.387
C7a-N1-N2	105.5	105.6	105.4	105.8
N1-N2-C3	113.8	113.8	113.8	115.1
N2-C3-C3a	105.8	105.8	105.9	105.4
C7a-N7-C6	115.6	115.7	115.9	115.5
N7-C6-C5	122.7	122.3	122.4	123.8
C6-C5-C4	123.3	123.6	123.4	120.8
C5-C4-C3a	109.8	109.8	109.8	117.7
C4-C3a-C7a	109.8	121.2	121.1	117.7
C3a-C7a-N7	121.4	121.4	121.6	123.5
N1-C7a-N7	128.3	128.2	127.8	127.3
C4-C3a-C7a-N7	179.3	1.8	1.3	-2.2
N1-N2-C3-C3a	0.4	0.3	0.0	0.2
N7-C6-C5-C4	0.5	0.2	1.2	0.7
C6-C5-C4-C(Ar2)	105.3	105.2	104.9	179.9
C4-C5-C6-C(Ar3)	-177.2	-177.5	-177.8	-179.6
N1-N2-C3-C(Ar1)	179.3	178.8	178.6	179.0

Table 6

Semiempirical calculation analysis (AM1 and MINDO/3)
for compounds **3** and **4**

	AM1		MINDO/3	
Tautomer	E(eV)	ΔH_f(Kcal/mol)	E(eV)	ΔH_f(Kcal/mol)
3a	210.47471	-4271.56118	147.15487	-4201.02431
4a	201.16721	-4271.96473	146.57906	-4101.05045
3b	197.13656	-4427.67713	141.45729	-4357.68142
4b	191.34234	-4428.06345	139.54147	-4357.76447
3c	166.63103	-4747.68214	99.79612	-4669.14063
4c	163.01148	-4747.83909	97.96135	-4669.22025
3d	199.34732	-4631.91256	139.50499	-4533.77815
4d	194.28234	-4632.06307	138.01834	-4533.84262

farther from the plane that those found for **4** also supports the theory that the phenyl ring at C3 influences the stability of the 2*H* tautomer through delocalization with the pyrazole ring.

EXPERIMENTAL

Melting points were taken on a Buchi Melting Point Apparatus and are uncorrected. The ^{1}H- and ^{13}C-NMR spectra were run on a Bruker DPX-300 spectrometer operating at 300 MHz and 75 MHz respectively, in DMSO-d_6 as solvent and TMS as internal reference. The mass spectra (ms) were scanned on a Hewlett Packard HP Engine-5959 spectrometer (equipped with a direct inlet probe) operating at 70 eV. The elemental analyses were obtained using a LECO CHNS-900 equipment. α-Cyanochalcones **2** were obtained by a modification of a previous method [28].

General Procedure for the Preparation of 3,4-Diaryl-5-cyano-4,7-dihydro-6-phenyl-2*H*-pyrazolo[3,4-*b*]pyridin*e* **4a-k**.

A solution of 1.40 mmoles of the corresponding 3-amino-5-arylpyrazole **1** and 1.40 mmoles of α-cyanochalcone **2** were heated to reflux in 50 mL of absolute ethanol for 1-2 hours (tlc control). After cooling down, the reaction mixture was allowed to stand overnight. The resulting precipitate was collected by filtration, washed with cold ethanol and then recrystallized from ethanol.

4-(4-Chlorophenyl)-5-cyano-4,7-dihydro-3,6-diphenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4a**).

Compound **4a** was obtained in 75% yield, mp 238°. Ms: EI m/z (relative abundance) = 408 (M^+), 298 (10), 297 (48, M^+-4-ClC_6H_4), 268 (12), 77 (18), 51 (7), 44 (93), 43 (12), 40 (100).

Anal. Calcd. for $C_{25}H_{17}N_4Cl$: C, 73.44; H, 4.19; N, 13.70. Found: C, 73.56; H, 4.12; N, 13.61.

4-(4-Chlorophenyl)-5-cyano-4,7-dihydro-3-(4-methylphenyl)-6-phenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4b**).

Compound **4b** was obtained in 83% yield, mp 268°. Ms: EI m/z (relative abundance) = 424/422 (6/22, M^+), 423 (8), 312 (29), 311 (100, M^+-4-ClC_6H_4), 91 (5).

Anal. Calcd. for $C_{26}H_{19}N_4Cl$: C, 73.84; H, 4.77; N, 13.25. Found: C, 73.59; H, 4.63; N, 13.33.

4-(4-Chlorophenyl)-5-cyano-4,7-dihydro-3-(4-methoxyphenyl)-6-phenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4c**).

Compound **4c** was obtained in 70% yield, mp 265°. Ms: EI m/z (relative abundance) = 440/438 (9/48, M^+), 439 (10), 329 (6), 328 (28), 327 (100, M^+-4-ClC_6H_4), 284 (6), 77 (6), 66 (7).

Anal. Calcd. for $C_{26}H_{19}N_4OCl$: C, 70.98; H, 4.58; N, 12.74. Found: C, 70.82; H, 4.62; N, 12.69.

3,4-Bis(4-chlorophenyl)-5-cyano-4,7-dihydro-6-phenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4d**).

Compound **4d** was obtained in 78% yield, mp 296°. Ms: EI m/z (relative abundance) = 446/444/442 (3/28/81, M^+), 445 (13), 443 (61), 441 (100), 408 (14), 407 (20), 406 (38), 405 (35), 342 (13), 341 (10), 334 (9), 333 (17), 332 (21), 185 (9), 77 (10).

Anal. Calcd. for $C_{25}H_{16}N_4Cl_2$: C, 67.73; H, 3.64; N, 12.64. Found: C, 67.71; H, 3.73; N, 12.54.

3-(4-Bromophenyl)-4-(4-chlorophenyl)-5-cyano-4,7-dihydro-6-phenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4e**).

Compound **4e** was obtained in 80% yield, mp 165°. Ms: EI m/z (relative abundance) = 489 (11), 488 (31), 487 (44), 486 (100, M^+), 485 (51), 484 (88), 483 (23), 452 (13), 451 (33), 450 (12), 449 (33), 369 (13), 342 (15), 341 (15), 105 (30), 77 (19), 76 (10), 51 (10).

Anal. Calcd. for $C_{25}H_{16}N_4BrCl$: C, 61.56; H, 3.31; N, 11.49. Found: C, 61.56; H, 3.59; N, 11.37.

4-(4-Chlorophenyl)-5-cyano-4,7-dihydro-3-(4-nitrophenyl)-6-phenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4f**).

Compound **4f** was obtained in 67% yield, mp 310°. Ms: EI m/z (relative abundance) = 456 (10), 455/453 (20/65, M^+), 454 (65), 452 (81), 451 (93), 450 (18), 417 (42), 416 (42), 405 (13), 404 (13), 371 (20), 370 (32), 344 (42), 343 (100, M^+-4-$O_2NC_6H_4$), 342 (79), 297 (19), 296 (17), 77 (8), 51 (9).

Anal. Calcd. for $C_{25}H_{16}N_5O_2Cl$: C, 66.15; H, 3.55; N, 15.44. Found: C, 65.93; H, 3.71; N, 15.52.

Table 7

Crystal analysis details

	4b	**4f**	**4i**	**6d**
Crystal Data				
Formula	$C_{55}H_{45}Cl_2N_9O$	$C_{27}H_{22}ClN_5O_3$	$C_{26}H_{20}N_4O$	$C_{26}H_{14}ClN_4$
Crystal habit	Colourless blocks	Colourless blocks	Colourless blocks	Colourless plates
Crystal size (mm)	0.20, 0.20, 0.15	0.30, 0.15, 0.10	0.15, 0.15, 0.12	0.10, 0.10, 0.05
Space group	Triclinic, $P\bar{1}$	Triclinic, $P\bar{1}$	Monoclinic, C2/c	Monoclinic, $P2_1/n$
Unit cell dimensions				
a (Å)	12.4124(5)	11.0809(4)	15.6264(3)	6.6222(5)
b (Å)	13.8275(4)	12.8703(4)	12.4397(2)	11.0791(10)
c (Å)	14.3744(6)	16.8439(4)	21.1296(4)	28.264(2)
α (°)	91.747(2)	81.5416(18)	90.00	90.00
β (°)	106.6376(17)	87.3861(18)	91.4371(9)	96.248(5)
γ (°)	99.610(2)	85.3010(15)	90.00	90.00
V(Å^3), Z	2322.64(15), 2	2366.70(13), 4	4106.04(13), 8	2061.3(3), 4
D_x(g/cm^3), M_r	1.314, 459.46	1.403, 499.95	1.309, 404.46	1.422, 441.31
F(000), μ(mm^{-1})	960, 0.192	1040, 0.202	1696, 0.082	904, 0.336
Data Collection				
Number of reflections				
Measured	36207	34427	47030	15117
Independent	10310	8341	3620	4026
Observed [I > 2σ(I)]	4898	6481	3086	1975
T (K)	150	150	150	150
R_{int}	0.1120	0.065	0.0740	0.047
θ_{min}...θ_{max}	1.48.....27.30°	1.22.....25.03°	1.92.....24.98°	2.34.....26.29°
h_{min}.....h_{max}	-16....16	-13....13	-18....18	-8....8
k_{min}.....k_{max}	-17....17	-15....15	-14....14	-11....13
l_{min}.....l_{max}	-18....18	-19....20	-25....25	-32....35
Refinement *(F^2)*				
R[F^2 > 2σ(F^2)]	0.0616	0.0947	0.0477	0.0576
WR(F^2)	0.1621	0.2967	0.1289	0.1150
S	0.934	1.137	1.056	0.935
Weighting-Scheme	ω = 1/[σ^2(F^2) +	ω = 1/[σ^2(F^2) +	ω = 1/[σ^2(F^2) +	ω = 1/[σ^2(F^2) +
P = (F$_o^2$ + 2F$_c^2$)/3	(0.0726P)^2]	(0.0885P)^2 + 21.2704]	(0.0653P)^2 + 4.5942P]	(0.0409P)^2]
$(\Delta/\sigma)_{max}$	0.001	0.001	0.001	0.001
Parameters	606	653	282	280
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (e Å^{-3})	-0.38, 0.49	-0.57, 1.23	-0.34, 0.39	-0.28, 0.40

5-Cyano-4,7-dihydro-3,4,6-triphenyl-2*H*-pyrazolo[3,4-*b*]-pyridine (**4g**).

Compound **4g** was obtained in 60% yield, mp 278°. Ms: EI m/z (relative abundance) = 376 (6), 375 (20), 374 (32, M$^+$), 299 (14), 298 (58), 297 (100, M$^+$-C$_6$H$_5$), 77 (19), 51 (91).

Anal. Calcd. for $C_{25}H_{18}N_4$: C, 80.19; H, 4.84; N, 14.96. Found: C, 80.11; H, 4.75; N, 15.02.

5-Cyano-4,7-dihydro-4-(4-methylphenyl)-3,6-diphenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4h**).

Compound **4h** was obtained in 56% yield, mp 320°. Ms: EI m/z (relative abundance) = 389 (10), 388 (30, M$^+$), 298 (22), 297 (100, M$^+$-4-CH$_3$C$_6$H$_4$), 77 (6).

Anal. Calcd. for $C_{26}H_{20}N_4$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.45; H, 5.26; N, 14.31.

5-Cyano-4,7-dihydro-4-(4-methoxyphenyl)-3,6-diphenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4i**).

Compound **4i** was obtained in 56% yield, mp 215°. Ms: EI m/z (relative abundance) = 405 (17), 404 (56, M$^+$), 403 (9), 298 (26), 297 (100, M$^+$-4-CH$_3$OC$_6$H$_4$), 77 (8).

Anal. Calcd. for $C_{26}H_{20}N_4O$: C, 77.21; H, 4.98; N, 13.85. Found: C, 77.30; H, 4.87; N, 13.79.

4-(4-Bromophenyl)-5-cyano-4,7-dihydro-3,6-diphenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4j**).

Compound **4j** was obtained in 74% yield, mp 266°. Ms: EI m/z (relative abundance) = 454/452 (11/13, M$^+$), 453 (5), 298 (27), 297 (100, M$^+$-4-BrC$_6$H$_4$), 77 (10).

Anal. Calcd. for $C_{25}H_{17}N_4$: C, 66.23; H, 3.78; N, 12.36. Found: C, 66.29; H, 3.70; N, 12.44.

5-Cyano-4,7-dihydro-4-(4-nitrophenyl)-3,6-diphenyl-2*H*-pyrazolo[3,4-*b*]pyridine (**4k**).

Compound **4k** was obtained in 75% yield, mp 200°. Ms: EI m/z (relative abundance) = 420 (6), 419 (22, M$^+$), 418 (7), 417 (14), 370 (8), 298 (24), 297 (100, M$^+$-4-O$_2$NC$_6$H$_4$), 77 (11).

Anal. Calcd. for $C_{25}H_{17}N_5O_2$: C, 71.59; H, 4.08; N, 16.70. Found: C, 71.67; H, 4.17; N, 16.63.

3,4-Bis(4-chlorophenyl)-5-cyano-6-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine (**6d**).

Similar to the general procedure after 24 hours of heating. Yield 70%, mp 290°. Ms: EI m/z (relative abundance) = 444/442/440 (13/74/100, M$^+$) 443 (21), 441 (22,), 439 (33), 407 (17), 406 (16), 405 (56), 342 (14), 341 (15). ^{1}H-nmr: 7.05 (d, 2H), 7.19 (d, 2H), 7.38 (s, 4H), 7.58-7.62 (m, 3H), 7.91-7.96 (m,

2H), 7.40-7.60 (s, 1H, deuterium exchangeable), ^{13}C-nmr: 100.7, 109.7, 117.6, 127.4, 128.0, 128.3, 129.2, 129.9, 130.4, 130.8, 131.1, 132.5, 132.8, 134.6, 137.6, 144.8, 150.5, 152.2, 159.9. *Anal*. Calcd. for $C_{25}H_{14}N_4Cl_2$: C, 68.04; H, 3.20; N, 12.70. Found: C, 67.75; H, 3.53; N, 12.75.

X-ray Analysis.

Crystal data and refinement details are displayed in Table 7. X-ray data were collected at the EPSRC, X-ray Crystallographic Service, University of Southampton using a Enraf Nonius Kappa-CCD diffractometer [29] using a fine-focus sealed x-ray tube Mo $K\sigma$ radiation (0.71073 Å) with a graphite oriented monochromator. Absorption corrections are performed by the Sortav package [30]. Low temperature data were collected using Oxford Cryosystems cryostream [31].

All the structures were solved by direct methods, and refined by least-squares procedure on the full matrix of squared Fobs (SHELX-97 [32]). Extinction corrections were not required. The hydrogens attached to the N atoms were located unequivocally on difference maps and then included as riding atoms in calculated positions, the remaining hydrogens were inserted by SHELXL and treated as riding atoms. All the H atoms were refined isotropically in the last cycles. The scattering factors were taken from International Tables for X-ray crystallography. Molecular graphics and geometrical analysis were done using PLATON-99 [33].

Complete data for **4b,i** and **6d** can be obtained on-line as CIF-ACCESS paper

IUC9900168/1-3 at www.iucr.ac.uk. Data for **4f** were deposited in the Crystallographic Cambridge Database , deposition number CCDC 136761.

Acknowledgements.

The authors thank The Colombian Institute for Science and Research (COLCIENCIAS, Project 1106-05-411-95) and UNIVERSIDAD DEL VALLE for financial support. The authors also thank the staff at the EPSRC, X-ray Crystallographic Service, University of Southampton, for the data collection.

REFERENCES AND NOTES

[1] C. R. Hardy, *Adv. Heterocyclic Chem.*, **36**, 343 (1984).

[2] R. E. Orth, *J. Pharm. Sci.*, **57**, 537 (1968), and references cited therein.

[3] M. H. Elnagdi, M. R. H. Elmoghayar, G. E. H. Elgemeie, *Adv. Heterocyclic Chem.*, **41**, 319 (1987).

[4] M. H. Elnagdi, M. R. H. Elmoghayar, K. U. Sadek, *Adv. Heterocyclic Chem.*, **48**, 223 (1990).

[5] Y. L. Chen, International Patent WO 9534563 A1 (1995); *Chem. Abstr.*, **124**, 232447 (1995).

[6] M. Masui, M. Kawakami, M. Nakajima, S. Hara, H. Ito, M. Ueda, *Drug. Dev. Res.*, **20**, 453 (1990).

[7] Y. Inagaki, S. Ono, K. Adachi, Jpn. Kokai Tokkyo Koho JP 63301882 A2, (1988); *Chem. Abstr.*, **111**, 155874 (1989).

[8] V. D. Orlov, J. Quiroga, N. N. Kolos, *Khim. Geterosikl. Soedin.*, 1247 (1987).

[9] V. D. Orlov, J. Quiroga, N. N. Kolos, S. M. Desenko, *Khim. Geterosikl. Soedin.*, 962 (1988).

[10] J. Quiroga, B. Insuasty, R. Rincón, M. Larrahondo, N. Hanold, H. Meier, *J. Heterocyclic Chem.*, **31**, 1333 (1994.)

[11] J. Quiroga, B. Insuasty, M. Marín, A. Aguirre, H. Meier, *Rev. Col. Quim.*, **21**, 29 (1992).

[12] J. Quiroga, A. Hormaza, B. Insuasty, C. Saitz, C. Jullian, A. Cañete, *J. Heterocyclic Chem.*, **35**, 61 (1998).

[13] J. Quiroga, B. Insuasty, S. Cruz, P. Hernandez, A. Bolaños, R. Moreno, A. Hormaza, R. H. de Almeida, *J. Heterocyclic Chem.*, **35**, 333 (1998).

[14] J. Quiroga, A. Hormaza, B. Insuasty, M. Marquez, *J. Heterocyclic Chem.*, **35**, 409 (1998).

[15] J. Quiroga, A. Hormaza, B. Insuasty, C. Saitz, C. Jullian, *J. Heterocyclic Chem.*, **35**, 575 (1998).

[16] J. Quiroga, B. Insuasty, A. Hormaza, D. Gamenara, L. Domínguez, J. Saldaña, *J. Heterocyclic Chem.*, **36**, 11 (1999).

[17] J. Quiroga, B. Insuasty, A. Hormaza, P. Cabildo, R. M. Claramunt, J. Elguero, *Heterocyclic Commun.*, **5** (2), 115 (1999).

[18] Y. Verdecia, M. Suárez, A. Morales, E. Rodríguez, E. Ochoa, L. González, N. Martín, M. Quinteiro, C. Seoane, J. L. Soto, *J. Chem. Soc., Perkin Trans. 1*, 947 (1996).

[19] M. K. Bernard, U. Wrzeciono, *J. Prakt. Chem.*, **331**, 600 (1989).

[20] Y. Kurasawa, Y. Kamigaki, H. Sik Kim, K. Yonekura, A. Takada, *J. Heterocyclic Chem*., **26**, 869 (1989).

[21] Y. Kurasawa, A. Takada, H. Sik Kim, Y. Okamoto, *J. Heterocyclic Chem.*, **30**, 1659 (1993).

[22] W. Holzer, K. Mereiter, B. Plagens, *Heterocycles*, **50**, 799 (1999).

[23] D. Cremer, J. A. Pople, *J. Am. Chem. Soc.*, **97**, 1354 (1975).

[24] J. C. A. Boeyens, *J. Cryst. Mol. Struct.*, **8**, 317 (1978).

[25] J. J. P. Stewart, *J. Comput.-Aided Mol. Des.*, **4**, 1 (1990).

[26] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).

[27] R. C. Bingham, M. J. S. Dewar, D. H. Lo, *J. Am. Chem. Soc.*, **97**, 1285-1302 (1975).

[28] S. Abdallah-El Ayoubi, F. Texier-Boullet, J. Hamelin, *Synthesis*, 258 (1994).

[29] Computing data collection: B.V. Nonius, "Kappa-CCD server software", Delft, The Netherlands, 1997. Z. Otwinowski, W. Minor, Computing cell refinement and data reduction, DENZO: "Methods in enzymology", Holland, 1997, pp 276, 307-326.

[30] R. H. Blessing, *Acta Cryst*., **A51**, 33-71 (1995); R. H. Blessing, *J. Appl. Cryst.*, **30**, 421-6 (1997).

[31] J. Cosier, A.M. Glazer, *J. Appl. Cryst.*, **19**, 105 (1986).

[32] G. M. Sheldrick, "SHELX-97. Program for the solution and refinement of crystal structures". University of Göttigen, Germany. 1997.

[33] A. L. Spek, "PLATON Molecular Geometry and Graphics Program, ver.1999", University of Utrecht, Utrecht, Holland, 1999.