SYNTHESIS, MOLECULAR STRUCTURE AND TAUTOMERISM OF 1(2)*H*-DIHYDROPYRAZOLO[3,4-*b*]PYRIDIN-6-ONES

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Abstract : Six 1(2)*H*-3-aryl-4-*p*-chlorophenyl-dihydropyrazolo[3,4-*b*]pyridin-6-ones have been prepared from the corresponding arylaminopyrazoles. The NMR study of these compounds reveals that all of them exist as 2*H*-tautomers in solution (DMSO-d_6) as well and in the solid state.

Introduction

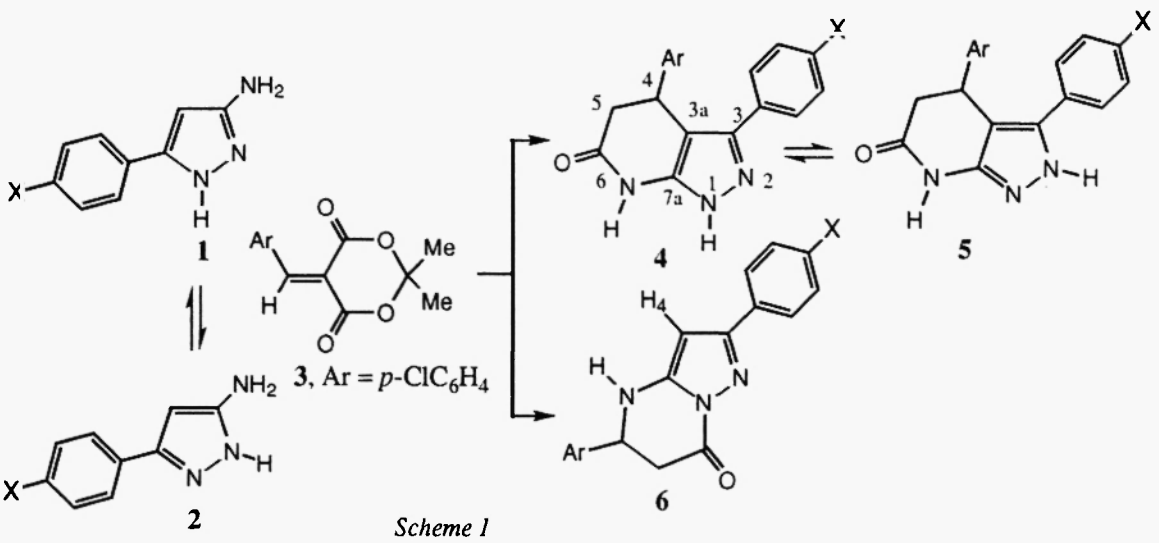
The reaction of 3(5)-aminopyrazoles with benzaldehydes and Meldrum's acid directly or preparing first the Meldrum's acid benzylidene derivative (**3**), has been studied by some of us in the case of 5-amino-1-aryl-3-methylpyrazoles.[1] With *N*-unsubstituted pyrazoles (**1**) or (**2**), the reaction, in principle, can afford two derivatives: a dihydropyrazolo[3,4-*b*]pyridin-6-one (**4**) or (**5**) (similar to that obtained previously with 1-aryl derivatives)[1] or a dihydropyrazolo[1,5-*a*]pyrimidine (**6**), like in the case of the compounds prepared from methyl orthoformate, Meldrum's acid and NH-pyrazoles.[2]

The absence of H_4 excludes structure **6**; it remains to determine the tautomerism and properties of the 3-aryl-4-*p*-chlorophenyl-dihydropyrazolo[3,4-*b*]pyridin-6-ones (**4**) or (**5**). The starting aminopyrazoles (**1/2**) present an interesting case of tautomerism: depending on the substituent X (**a** H, **b** CH_3, **c** OCH_3, **d** Cl, **e** Br, **f** NO_2) the most stable tautomer is the 3-amino-5-aryl (**1**) or the 5-amino-3-arylpyrazole (**2**).[3] Therefore, it was interesting to determine the tautomeric structure, (**4**) or (**5**), of the resulting cyclic compound and to compare it with that of the starting material, (**1**) or (**2**).

Results and Discussion

Synthesis

Compounds (**4/5**) were prepared by reaction of the corresponding 1*H*-3(5)-amino-5(3)-arylpyrazoles (**1a/2a**)-(**1f/2f**) with *p*-chlorobenzaldehyde and Meldrum's acid in ethanol.



Scheme 1

^1H and ^{13}C NMR spectroscopy in solution

The ^1H and ^{13}C NMR spectra are gathered in Tables 1 and 2. The ^{13}C results will be discussed in relation with the tautomerism. The first order analysis of the ABC system formed by the protons of positions 4 and 5 yield three coupling constants, a geminal (15.8-15.9 Hz) and two vicinal ones (7.4-7.6 and 1.8 Hz). The application of Karplus equations [$^3J_{vic} = 8.5 \cos^2\phi - 0.3$ (for $0° \leq \phi \leq 90°$) and $^3J_{vic} = 9.5 \cos^2\phi - 0.3$ (for $90° \leq \phi \leq 180°$)][4,5] leads to two dihedral angles 80° (for 1.8 Hz) and 140° (for 7.5 Hz). These values identified H-5a and H-5e and established that the 4-*p*-chlorophenyl group is in a pseudo-equatorial position.

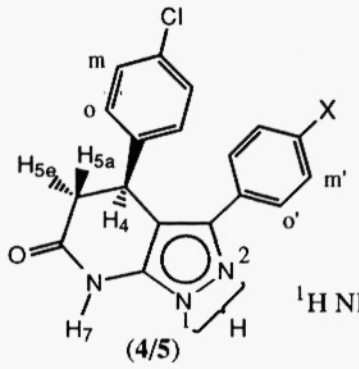
^{13}C NMR spectroscopy in the solid state (CPMAS)

The solid state chemical shifts for compounds **4a/5a** and **4f/5f** are also reported in Table 2. As it can be seen, they are very similar to those found in DMSO-d_6 solution. Moreover, no significant splitting is observed pointing to the presence of only one tautomer in the solid state.

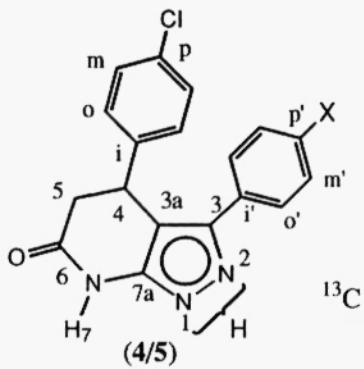
Tautomerism.

In DMSO-d_6 solution, compound (**4a/5a**) was sparsely soluble and a small amount of trifluoroacetic acid had to be added. By internal comparison and considering the aromatic substituent chemical shifts (SCS)[6] and the chemical shifts of phenylpyrazoles[7] it is possible to estimate, with a reasonable accuracy, the ^{13}C chemical shifts of the 3-phenyl group for compound (**4a/5a**) in pure DMSO-d_6:

Table 1. ^{1}H NMR chemical shifts (δ in ppm) and coupling constants (J in Hz) of 3-(4-X-phenyl)-4-(4-chlorophenyl)-4,5,6,7-tetrahydropyrazolo [3,4-*b*]pyridin-6-ones



^{1}H NMR



^{13}C NMR

Comp.	$H_{1(2)}$	H_4	H_{5a}	H_{5e}	H_7	H_o	H_m	$H_{o'}$	$H_{m'}$	X
(**a**), X = H	c	4.47(dd)	3.05(dd)	d	10.54(s)	7.25-7.41	7.11(d)	7.25-7.41	7.25-7.41	7.25-7.41
b		^3J= 7.5	J_{gem}= 15.9			(m)	^3J= 8.3	(m)	(m)	(m)
		^3J= 1.8	^3J= 7.5							
(**b**), X = Me	12.61(s)	4.48(dd)	3.06(dd)	2.46(d)	10.49(s)	7.34 (d)	7.13(d)	7.32(d)	7.17(d)	2.26(s)
		^3J= 7.5	J_{gem}= 15.9	^3J= 1.8		^3J= 8.4		^3J= 8.0		
a		^3J= 1.8	^3J= 7.5							
	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
b	11.50(s)	4.46(dd)	3.05(dd)	2.47(d)	10.50(s)	7.29(d)	7.11(d)	7.30(d)	7.14(d)	2.24(s)
		^3J= 7.5	J_{gem}= 15.9	^3J= 1.8		^3J= 8.4		^3J= 8.0		
		^3J= 1.8	^3J= 7.5							

(c), X = OMe a	12.54(s)	4.46(dd) ^3J= 7.4 ^3J= 1 8	3.06(dd) Jgem= 15.9 ^3J= 7.4	d	10.47(s)	7.34 (d) ^3J= 8.4	7.13(d)	6.94(d) ^3J= 8.7	7.34(d)	3.73(s)
(d), X = Cl a	12.74(s)	4.51(dd) ^3J= 7.4 ^3J= 1 8	3.06(dd) Jgem= 15.9 J= 7.4	2.47(d) ^3J= 1.8	10.53(s)	7.34 (d) ^3J= 8.4	7.12(d)	7.40-7.47 (m)	7.40-7.47 (m)	—
(e), X = Br a	12.75(s)	4.50(dd) ^3J =7.4 ^3J =1.8	3.06(dd) Jgem= 15.9 ^3J= 7.4	2.47(d) ^3J= 1.8	10.54(s)	7.34 (d) ^3J= 8.4	7.12(d)	7.58(d) ^3J= 8.5	7.36(d)	—
(f), X = NO_2 a	13.05(s)	4.61(d) ^3J= 7.6 ^3J= 1.8	3.20(dd) Jgem= 15.8 ^3J= 7.6	2.54(d) ^3J= 1.8	10.63(s)	7.34 (d) ^3J= 8.4	7.14(d)	7.70(d) ^3J= 8.7	8.23(d)	—

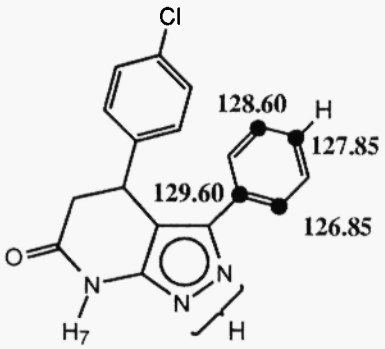
[a] In DMSO-d_6; [b] In DMSO-d_6 plus a drop of CF_3CO_2H;[c] not observed; [d] masked by the solvent signal.

Tab'e 2. ^{13}C Chemicai Shifts (δ in ppni) and Coupling Constants (J in Hz) of 3-(4-X-phenyl)-4-(4-chlorophenyl)-4,5,6,7-tetrahydropyrazolo [3,4-*b*]pyridin-6-ones

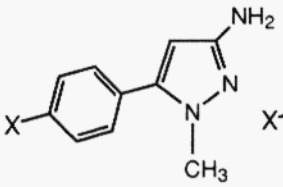
	dihydiopyrazolo[3 4-*b*]pyridin-6-one						4-Ar = *p*-chloroph:nyl				3-Ar = *p* -X-ph:nyl				
Comp.	C_3	C_{3a}	C_4	C_5	C_6	C_{7a}	C_i	C_o	C_m	C_p	$C_{i'}$	$C_{o'}$	$C_{m'}$	$C_{p'}$	X
(a) X = H b	143.0	101.6	34.2 ^1J=135.4	41.4 ^1J=130 2	169.6	150.3	138.7	129 3 ^1J=162.0	128.7 ^1J=161.9 ^3J=7.1	132.0	129.6	126.5 ^1J=159.8 ^3J=6 3	129.4 ^1J=161.7	129 2 ^1J=162.0	—
(a) X = H c	142.8	101.7	32.3	43.2	172.3	150.1	140 2	128 9	128 9	128.9	128.9	128 9	128.9	128.9	—

(b) X = CH_3 a	142.7	100.7	33.6 ^1J=134.5	40.9 ^1J=131.0	169.0	150.1	137.7	128.8 ^1J=162.3	128.7 ^1J=167.1	131.3	126.4	125.7 ^1J=159.4 ^3J=6.3	128.7 ^1J=167.1	137.7	CH_3 20.8 ^1J=126.4
b	142.9	101.1	34.0	41.2	169.4	150.1	138.6	129.8	129.1	131.8	126.7	126.3	129.0	138.3	20.9
(c) X = OCH_3 a	142.7	100.1	33.5 ^1J=135.1	40.9 ^1J=131.0	168.9	150.0	137.5	127.1 ^1J=159.2 ^3J=7.5	128.7 ^1J=166.3	131.2	121.7	128.7 ^1J=166.3 ?	114.4 ^1J=160.8 ^3J=4.3	159.1	OCH_3 55.2 ^1J=144.4
(d) X = Cl a	142.3	101.4	33.4 ^1J=130.0	40.8 ^1J=129.5	168.8	150.2	136.5	127.5 ^1J=162.8 ^3J=6.1	128.7 ^1J=165	131.3	128.0	129.0 ^1J=168.1	128.6 ^1J=164.9	132.7	—
(e) X = Br a	142.3	101.4	33.5 ^1J=135.5	40.8 ^1J=131.2	168.9	150.2	136.6	127.8 ^1J=160.9 ^3J=6.1	128.7 ^1J=167.6	131.4	128.3	128.8 ^1J=167.6	131.9 ^1J=167.9	121.4	—
(f) X = NO_2 a	142.0	103.0	33.5 ^1J=139.2	40.6 ^1J=131.0	168.7	142.0	150.5	126.6 ^1J=164.8 ^3J=6.5	128.7 ^1J=168.6	131.4	135.2	128.8 ^1J= ^3J=4.9	124.2 ^1J=170.1 ^3J=3.2	146.5	—
(f) X = NO_2 c	139.6	101.2	31.9	40.4	172.3	139.6	149.0	127.2	127.2	133.8	135.3	129.5	124.0	147.1	—

[a] DMSO-d_6; [b] DMSO-d_6 plus a drop of CF_3CO_2H; [c] Solid state ^{13}C CPMAS NMR.



4a/5a



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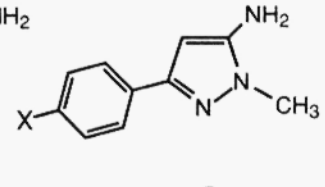

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Comparing now the ^{13}C chemical shifts of the 3-aryl groups in compounds (**4/5**) with those of the *N*-methyl derivatives **7** and **8** of (**1**) and (**2**) (to avoid tautomerism)[3] it results in two Equations:

$$\delta(\mathbf{4/5}) = -1.2 + 1.005\ \delta(\mathbf{7}),\ n = 24,\ r^2 = 0.992 \quad (1)$$

$$\delta(\mathbf{4/5}) = 11.1 + 0.913\ \delta(\mathbf{8}),\ n = 24,\ r^2 = 0.888 \quad (2)$$

The much better correlation coefficient and the slope close to 1 demonstrates that bicycles (**4/5**) are similar to 5-arylpyrazoles **7**, therefore, that all the bicycles are 5-aryl derivatives, i.e. (**5**) tautomers. In the solid state, the ^{13}C CPMAS spectra of compounds **a** and **f** yield chemical shifts very similar to those in solution (Table 2). Therefore, all these compounds exist in the solid state as 2*H*-tautomers (**5**).

Conclusion

It is now possible to compare the aminopyrazoles (**1/2**)[3] with the bicycles (**4/5**) in what concerns tautomerism (see Table 3).

Table 3. Comparison of the tautomerism of pyrazoles and dihydropyrazolo[3,4-*b*]pyridin-6-ones

	Pyrazoles		Dihydropyrazolo[3,4-*b*]pyridin-6-ones	
	DMSO-d_6	Solid state	DMSO-d_6	Solid state
a, X = H	54% (**1**)	(**1**)	100% (**5**)	(**5**)
b, X = CH_3	58% (**1**)	(**1**)	100% (**5**)	(**5**)
c, X = OCH_3	55% (**1**)	(**1**)	100% (**5**)	(**5**)
d, X = Cl	42% (**1**)	(**1**)	100% (**5**)	(**5**)
e, X = Br	34% (**1**)	(**1+2**)	100% (**5**)	(**5**)
f, X = NO_2	~1% (**1**)	(**2**)	100% (**5**)	(**5**)

The results of Table 3 show that in the case of pyrazoles the tendency to be at position 3 of the pyrazole is similar for the amino and aryl groups so that both tautomers are of similar energy and that modifications of X shift the equilibrium towards one or the other tautomer. In the case of dihydropyrazolo[3,4-*b*]pyridin-6-ones, the NH-CO-CH_2-R fragment always dominates over the aryl group and whatsoever X the only tautomer present is the 2*H* one (**5**). This difference cannot be adscribed to the cycle (only small cycles, through the Mills-Nixon effect, can shift the tautomeric equilibrium).[8-10] Therefore, it is the replacement of the NH_2 group for the more electron-withdrawing group NH-CO-R that shifts the equilibrium to the tautomer where this group is at position 3 of the pyrazole. This tendency has been found for other electron-withdrawing groups such as nitro, ammonio and diazonio.[11,12]

Experimental

Materials. Melting points were determined on Buchi 510 and Reichert-Thermovar instruments and are uncorrected. ^1H and ^{13}C FT-NMR spectra were recorded at 200 (400) and 50 (100) MHz on Bruker AC200 and AMX400 specrometers. The chemical shifts were measured relative to TMS. ^{13}C CPMAS NMR spectra were recorded at 100 MHz on a Bruker AC200 spectrometer with standard conditions.[3] The starting pyrazoles are described in ref. 3.

2H-3-phenyl-4-p-chlorophenyl-dihydropyrazolo[3,4-b]pyridin-6-one (**5a**). A solution of 1.59 g (0.01 mol) of 1*H*-5-amino-3-phenylpyrazole (**1a**), 1.40 g (0.01 mol) of *p*-chlorobenzaldehyde and 1.44 g (0.01 mol) of Meldrum's acid were heated in 20 ml of anhydrous ethanol during 15 min. After cooling, the precipitate was filtered off and washed with cold ethanol. The solid was crystallized in ethanol. Yield 75%, mp 365 °C. Anal. Calcd for $C_{18}H_{14}N_3OCl$: C, 66.77; H, 4.36; N, 12.98. Found: C, 66.65, H, 4.39, N, 12.84.

2H-3-p-methylphenyl-4-p-chlorophenyl-dihydropyrazolo[3,4-b]pyridin-6-one (**5b**). Using the same procedure but starting from 1*H*-5-amino-3-*p*-methylphenylpyrazole (**1b**). The solid was crystallized in ethanol. Yield 70%, mp 315 °C. Anal. Calcd for $C_{19}H_{16}N_3OCl$: C, 67.56; H, 4.77; N, 12.44. Found: C, 67.25, H, 4.59, N, 12.12.

2H-3-p-methoxyphenyl-4-p-chlorophenyl-dihydropyrazolo[3,4-b]pyridin-6-one (**5c**). Using the same procedure but starting from 1*H*-5-amino-3-*p*-methoxyphenylpyrazole (**1c**). The solid was crystallized in ethanol. Yield 68%, mp 295 °C. Anal. Calcd for $C_{19}H_{16}N_3O_2Cl$: C, 64.50; H, 4.56; N, 11.88. Found: C, 64.26, H, 4.61, N, 11.92.

2H-3-p-chlorophenyl-4-p-chlorophenyl-dihydropyrazolo[3,4-b]pyridin-6-one (**5d**). Using the same procedure but starting from 1*H*-5-amino-3-*p*-chlorophenylpyrazole (**1d**). The solid was crystallized in ethanol. Yield 75%, mp 350 °C. Anal. Calcd for $C_{18}H_{13}N_3OCl_2$: C, 60.35; H, 3.66; N, 11.76. Found: C, 60.55, H, 3.73, N, 11.59.

2H-3-p-bromophenyl-4-p-chlorophenyl-dihydropyrazolo[3,4-b]pyridin-6-one (**5e**). Using the same procedure but starting from 1*H*-5-amino-3-*p*-bromophenylpyrazole (**1e**). The solid was crystallized in ethanol. Yield 73%, mp 348 °C. Anal. Calcd for $C_{18}H_{13}N_3OClBr$: C, 53.69; H, 3.25; N, 10.44. Found: C, 53.75, H, 3.51, N, 10.17.

2H-3-p-nitrophenyl-4-p-chlorophenyl-dihydropyrazolo[3,4-b]pyridin-6-one (**5f**). Using the same procedure but starting from 1*H*-5-amino-3-*p*-nitrophenylpyrazole (**1f**). The solid was crystallized in ethanol. Yield 71%, mp 345 °C. Anal. Calcd for $C_{18}H_{13}N_4O_3Cl$: C, 64.86; H, 3.93; N, 16.81. Found: C, 64.64, H, 3.88, N, 16.73.

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References

(1) J. Quiroga, A. Hormaza, B. Insuasty and M. Márquez, J. Heterocycl. Chem. 35, 000 (1998).
(2) J. Quiroga, A. Hormaza, B. Insuasty, C. Saitz, C. Jullian and A. Cañete, J. Heterocycl. Chem. 35, 61 (1998).
(3) J. Quiroga Puello, B. Insuasty Obando, C. Foces-Foces, L. Infantes, R.M. Claramunt, P. Cabildo, J.A. Jiménez and J. Elguero, Tetrahedron 53, 10783 (1977).
(4) L.M. Jackman and S. Sternhell, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd Edition, Pergamon Press, Oxford, 1969, p. 281.
(5) J. Elguero and A. Fruchier, An. Quím. 70, 141 (1974).
(6) D.F. Ewing, Org. Magn. Reson. 12, 499 (1979).
(7) M. Begtrup, G. Boyer, P. Cabildo, C. Cativiela, R.M. Claramunt, J. Elguero, J.I. García, C. Toiron and P. Vedsø, Magn. Reson. Chem. 31, 107 (1993).
(8) A. Martínez, M.L. Jimeno, J. Elguero and A. Fruchier, New J. Chem. 18, 269 (1994).
(9) M. Ramos, I. Alkorta and J. Elguero, Tetrahedron 53, 1403 (1997).
(10) I. Alkorta and J. Elguero, Struct. Chem. 8, 189 (1997).
(11) C. Foces-Foces, A.L. Llamas-Saiz, M. Menéndez, N. Jagerovic and J. Elguero, J. Phys. Org. Chem. 10, 637 (1997).
(12) A.E. Hammadi, M.E. Mouhtadi, R. Notario, A. Werner and J. Elguero, J. Chem. Soc. Perkin trans. 2 379 (1995).

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