Conformation and *Ortho* Steric Effects in a Series of 2-(Pyrazol-1-yl)quinolines

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Nine 2-(pyrazol-1-yl)-4-methylquinolines bearing substituents on the pyrazole 3- or 5-positions (H, Me, Et, *i*-Pr, *t*-Bu) were regioselectively synthesized either using the direct condensation of 2-chloro-4-methylquinoline and sodium salt of 3(5)-substituted pyrazoles or by treatment of 2-hydrazino-4-methylquinoline with an appropriate β-ketoaldehyde. The ^{1}H and ^{13}C chemical shifts were discussed taking into account the preferred conformation about the C-2-N-1' bond as calculated by the AM1 Hamiltonian. It appears that 5-ethyl and 5-isopropyl substituted derivatives present short C-H···N-1 interactions. *Ortho* steric effects appear to be responsible for these conformations.

We have been interested, for a long time, in the conformation of systems related to biphenyl (atropisomerism) specially when the ortho positions are occupied by the sp^2 nitrogen atoms of azoles and azines [1-4]. For instance, the dihedral angle formed by the azole and the phenyl ring in a series of *N*-phenylazoles 1 was studied using the E.H.T. (Extended Hückel Theory) method and compared with experimental results: when R$_5$ = H, the dihedral angle φ for the minimum energy conformation is about 26°, while a methyl group at the 5-position increases the angle till 55° [1]. A series of *N,N*-linked biazoles, amongst them 2, were studied within the MNDO approximation: it was concluded that the C-H···N interaction was attractive and compound 2 adopts the *anti* conformation [2]. In a review of the effect of *N*-substituents on the ^{13}C nmr parameters of azoles [3], the *N*-phenyl series, to which compound 1 belongs, was discussed taking into account that carbons C$_{ortho}$ chemical shifts reflect the magnitude of the angle of twist between the phenyl and the azole rings. Finally, the problem of the existence of C(Ar)-H···N intramolecular hydrogen bonds was studied by X-ray crystallography and AM1 calculations in a series of azacarbazoles, for instance 3 [4].

Table 1

^{1}H NMR Chemical Shifts (ppm) and [1]H-[1]H Coupling Constants (Hz) of Compounds **4a-i** (solvent: deuteriochloroform)

	H-3	CH$_3$-4	H-5	H-6	H-7	H-8	H-3'	H-4'	H-5'	J$_{5,6}$	J$_{6,7}$	J$_{7,8}$	J$_{5,7}$	J$_{6,8}$	J$_{3',4'}$	J$_{4',5'}$
4a R$_3$ = R$_5$ = H	8.00	2.64	7.84	7.41	7.63	7.95	7.77	6.47	8.76	8.3	7.3	8.4	—	—	1.5	2.6
	(s)	(s)	(d)	(t)	(t)	(d)	(d)	(m)	(d)							
4b R$_3$ = Me	8.00	2.73	7.93	7.47	7.67	7.97	2.42	6.29	8.66	7.1	8.3	7.0	1.4	1.3	—	2.5
	(s)	(s)	(d)	(t)	(t)	(d)	(s)	(d)	(d)							
4c R$_3$ = Et	8.03	2.79	8.01	7.53	7.73	8.00	[a]	6.38	8.72	8.2	8.3	8.5	—	—	—	2.2
	(s)	(s)	(d)	(t)	(t)	(d)		(d)	(d)							
4d R$_3$ = *i*-Pr	7.96	2.74	7.82	7.47	7.68	8.02	[b]	6.35	8.67	8.2	8.3	9.1	1.2	1.4	—	2.6
	(s)	(s)	(d)	(t)	(t)	(d)		(d)	(d)							
4e R$_3$ = *t*-Bu	8.07	2.76	7.96	7.48	7.67	7.97	[c]	6.38	8.65	8.2	6.9	8.4	1.5	1.2	—	2.6
	(d)	(d)	(d)	(t)	(t)	(d)		(d)	(d)							
4f R$_5$ = Me	7.99	2.85	7.98	7.52	7.69	8.00	7.63	6.23	2.75	8.4	7.1	7.1	1.4	1.4	1.5	—
	(s)	(s)	(d)	(t)	(t)	(d)	(d)	(d)	(s)							
4g R$_5$ = Et	7.98	2.75	8.00	7.53	7.69	8.00	7.64	6.28	[d]	6.5	6.9	6.8	1.4	1.5	1.6	—
	(s)	(s)	(d)	(t)	(t)	(d)	(d)	(d)								
4h R$_5$ = *i*-Pr	7.94	2.72	7.93	7.51	7.67	7.97	7.61	6.27	[e]	6.7	6.9	7.1	1.1	1.6	1.6	—
	(s)	(s)	(d)	(t)	(t)	(d)	(d)	(d)								
4i R$_5$ = *t*-Bu	7.62	2.75	8.03	7.62	7.74	8.08	7.62	6.29	[f]	8.0	8.3	8.7	—	—	1.7	—
	(s)	(s)	(d)	(m)	(t)	(d)	(m)	(d)								

[a] 2.81 (CH$_2$CH$_3$), 1.38 (CH$_2$CH$_3$), J = 7.6. [b] 3.14 (CH(CH$_3$)$_2$), 1.37 (CH(CH$_3$)$_2$), J = 6.9. [c] 1.41 (C(CH$_3$)$_3$), J$_{H-3',CH_3}$ = 0.96 Hz. [d] 3.37 (CH$_2$CH$_3$), 1.35 (CH$_2$CH$_3$), J = 7.4. [e] 4.25 (CH(CH$_3$)$_2$), 1.30 (CH(CH$_3$)$_2$), J = 6.9. [f] 1.42 (C(CH$_3$)$_3$).

1   **2**   **3**
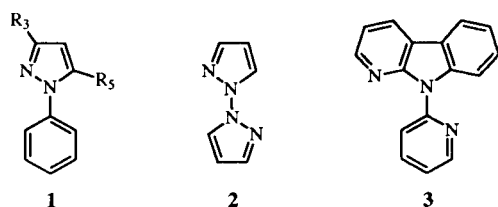
Results and Discussion.

Chemistry.

Synthesis of **4a** was readily achieved by treating 2-hydrazino-4-methylquinoline (**5**) with malonaldehyde bis(dimethyl acetal) whereas compounds **4b** and **4f** were obtained from **5** and acetylacetaldehyde dimethyl acetal, using a procedure previously described [5]. Similar treatment of **5** and β-ketoaldehydes afforded **4g-4i** as the exclusive products. Failure to get **4c-4e** even in minute amounts reflects the greater reactivity of aldehydic carbonyl. These isomers **4c-4e** were synthesized by the direct condensation of 2-chloro-4-methylquinoline **6** with the sodium salt of the corresponding 3(5)-alkylpyrazole. Regioselective formation of 3-substituted isomers, **4c-4e**, may be traced to steric reasons.

series **4h** are considerably deshielded with regard to the corresponding groups at position 3', **4b-4d**, while the *tert*-butyl is unaffected, **4i** *vs* **4e**. $^3J(^1H-^1H)$ Coupling constants of the pyrazole ring are characteristic of the substitution pattern [6] but hardly informative of the conformation.

The differences in chemical shifts for pairs of identically substituted isomers ($\Delta\delta H = \delta H\text{-}5 - \delta H\text{-}3$) are: methyl group, 0.33 ppm **4f-4b**, ethyl group, 0.56 ppm **4g-4c** and isopropyl group, 1.11 ppm **4h-4d**. These values can be corrected taking into account the number of protons: methyl group 0.99, ethyl group 1.12 and isopropyl group 1.11 ppm.

To understand these curious results, we have determined the ^{13}C chemical shifts of compounds **4a-4i** (Table 2) and calculated, within the AM1 approximation [7], the preferred conformation of these compounds (Table 3).

The results of Table 2 show the usual effect of substituents through bonds, for instance, $\delta C\text{-}2$ is sensitive to substituent R_3. Which is more interesting is that $\delta C\text{-}3$ is rather insensitive to R_3 (min 112.3, max 112.8 ppm) but very sensitive to R_5 (min 112.3, max 119.3). As we have reported in our review, this last effect is related to the torsion angle between aromatic planes, in compounds **4**, between pyrazole and quinoline planes.

Table 2

^{13}C NMR Chemical Shifts (ppm) of Compounds **4a-i** (solvent:deuteriochloroform)

Compound	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	Me-4	C-3'	C-4'	C-5'	R3,R5
4a $R_3,R_5 = H$	149.7	112.3	146.3	126.9	123.6	125.4	128.9	129.6	147.3	18.7	141.9	107.8	127.1	—
4b $R_3 = Me$	149.9	112.3	146.6	126.9	123.8	125.2	128.9	129.7	147.3	18.8	151.7	108.2	128.0	13.9 (CH$_3$)
4c $R_3 = Et$	157.8	112.5	146.8	127.0	123.8	125.3	128.9	129.8	147.3	18.9	150.0	106.8	127.9	21.8 (CH$_2$CH$_3$), 13.7 (CH$_2$CH$_3$)
4d $R_3 = i$-Pr	162.1	112.6	146.6	126.9	123.8	125.2	128.9	129.7	147.2	18.9	150.1	105.3	127.8	18.2 (CH(CH$_3$)$_2$), 27.7 (CH(CH$_3$)$_2$)
4e $R_3 = t$-Bu	164.7	112.8	146.7	126.9	123.8	125.2	128.9	129.7	147.1	19.0	150.3	105.0	127.5	32.5 (C(CH$_3$)$_3$), 30.4 (C(CH$_3$)$_3$)
4f $R_5 = Me$[a]	152.1	115.4	146.2	126.7	123.7	125.9	129.6	129.3	146.9	18.9	140.6	108.9	141.4	14.9 (CH$_3$)
4g $R_5 = Et$	152.1	115.7	146.3	126.7	123.7	127.8	129.6	129.3	146.9	18.9	140.6	107.1	147.8	21.8 (CH$_2$CH$_3$), 13.23 (CH$_2$CH$_3$)
4h $R_5 = i$-Pr	152.7	116.2	146.9	126.8	123.7	125.9	129.6	129.3	147.7	18.9	140.6	105.1	151.2	24.5 (CH(CH$_3$)$_2$), 22.8 (CH(CH$_3$)$_2$)
4i $R_5 = t$-Bu	153.1	119.3	145.9	127.4	123.7	126.6	129.5	129.7	147.1	18.8	139.9	105.6	154.0	32.6 (C(CH$_3$)$_3$), 30.6 (C(CH$_3$)$_3$)

[a] HMQC, 500 MHz.

4
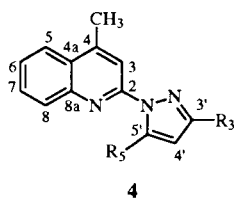
a,	$R_3 = R_5 = H$
b,	$R_3 = CH_3, R_5 = H$
c,	$R_3 = C_2H_5, R_5 = H$
d,	$R_3 = i\text{-}C_3H_7, R_5 = H$
e,	$R_3 = t\text{-}C_4H_9, R_5 = H$
f,	$R_3 = H, R_5 = CH_3$
g,	$R_3 = H, R = C_2H_5$
h,	$R_3 = H, R_5 = i\text{-}C_3H_7$
i,	$R_3 = H, R_5 = t\text{-}C_4H_9$

NMR Spectroscopy.

When ^1H nmr spectra of a series of nine 2-(pyrazol-1-yl)-4-methylquinolines **4a-4i** were recorded (Table 1) several interesting observations were made: i) the quinoline H-3 proton is rather insensitive to the presence of substituents at position 5 of the pyrazolyl substituent; ii) the C-H protons of the 5'-methyl **4f**, 5'-ethyl **4g** and 5'-*i*-propyl

The torsion angles ϕ of Table 3 corresponds to the conformations of minimum energy. For 5'-unsubstituted derivatives, **4a-4e**, the conformation is almost planar and the lone pairs are in an *anti* disposition:

4a-4e
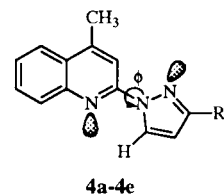
The introduction of substituents at position 5'-increases progressively the ϕ value and for the 5'-*tert*-butyl substituted derivative **4i**, the conformation although nearly perpendicular belongs to the *syn* class ($\phi > 90°$).
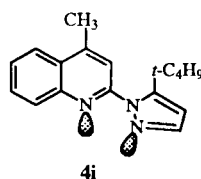
4i

Table 3

Result of the AM1 Calculations (ΔH_f in kcal mol^{-1})

Substituent		ϕ	ΔH_f
H	(4a)	0.4°	131.6
3-Me	(4b)	0.5°	124.0
3-Et	(4c)	0.6°	117.9
3-*i*-Pr	(4d)	0.5°	114.2
3-*t*-Bu	(4e)	0.4°	111.7
5-Me	(4f)	24.2°	124.9
5-Et	(4g)	37.0°	120.2
5-*i*-Pr	(4h)	42.2°	116.4
5-*t*-Bu	(4i)	97.1°	117.4

Table 4

Summary of AM1 Geometries, ^{13}C and ^{1}H Chemical Shifts (in ppm) and Steric $S°$ Parameters

5-R		ϕ	$\cos^2\phi$	δC-3	δH-3	$S°$
H	(4a)	0.4°	1.000	112.3	8.00	0
Me	(4f)	24.2°	0.832	115.4	7.99	-0.73
Et	(4g)	37.0°	0.638	115.7	7.98	-1.08
i-Pr	(4h)	42.2°	0.549	116.2	7.94	-1.44
t-Bu	(4i)	97.1°	0.015	119.3	7.62	-3.94

It has been established by Gallo, Roussel and Berg [8] that the description of steric *ortho* effects in heteroaromatic compounds requires a new steric parameter they named $S°$. On the other hand, torsional properties are better described by the square value of the angle cosines ($\cos^2\phi$) than by the angle ϕ itself [9-11]. We have calculated, using the data of Table 4, the regression equation relating $\cos^2\phi$ to $S°$ (ref [8], page 215) for compounds **4a, 4f-4i**:

$$\cos^2\phi = 0.96 \ (\pm0.04) + 0.25 \ (\pm0.0 \ 2) \ S°, \ n = 5, \ r^2 = 0.98 \ (1)$$

The very good correlation coefficient allows to conclude that, on one hand, the calculated ϕ values are reasonable approximation to the true conformation and, on the other, that $S°$ coefficients are convenient estimators of steric *ortho* effects.

As we have discussed above, δC-3 values are related to torsional effects, thus we tried the following equation:

$$\delta C\text{-}3 = 119.6 \ (\pm0.8) - 6.4 \ (\pm1.1) \cos^2\phi, \ n = 5, \ r^2 = 0.91 \ (2)$$

The correlation is a little worse (the 5-methyl derivative **4f** deviates) but still it constitutes a proof of the usefulness of *ortho* chemical shifts to evaluate torsion angles in biphenyl-type compounds. Although H-3 chemical shifts

are rather insensitive to substituents at position 5', we try the following equation:

$$\delta H\text{-}3 = 7.66 \ (\pm0.06) + 0.40 \ (\pm0.09) \cos^2\phi, \ n = 5, \ r^2 = 0.87 \ (3)$$

The slope, 0.4, corresponds to the very low sensitivity of H-3 to the conformation (the coefficient of the regression between δH-3 and $S°$ is better, $r^2 = 0.94$).

Thus, part of the problem has been conveniently rationalized by the AM1 calculations and the *ortho* aromatic steric effects. It remains to explain why the C(Ar)-C-H protons of 5'-substituents are strongly deshielded with regard to the corresponding signals in 3'-substituents. Looking at the calculated minimum energy conformations for the 5'-substituted derivatives it appears that the 5'-methyl one, **4f**, has one of the protons of the methyl group at 2.72 Å of the quinoline N-1 atom, the 5'-ethyl derivative, **4g**, has one of the protons of the methylene at 2.58 Å of the N-1 atom and, finally, the proton of the methine in the case of the 5'-isopropyl derivative, **4h**, is at 2.58 Å of the N-1 atom. This account satisfactorily for the values of methyl group 0.99, ethyl group 1.12 and isopropyl group 1.11 ppm.

EXPERIMENTAL

Melting points were determined with a Reichert Jung microscope apparatus and are uncorrected. Reagent and solvents were purchased from common commercial suppliers. The nmr spectra were recorded on Bruker AM-200 or Varian Gemini-200 spectrometers working at 200 and 50 MHz for ^{1}H and ^{13}C respectively. In all cases, TMS was used as internal standard. HMQC sequence [12] was performed on a Varian Unity-500 operating at 500 MHz. AM1 calculations were carried out with the AMPAC 5.0 package [13]. In all cases, full geometry optimization with the Fletcher-Powell algorithm and the PRECISE keyword were used.

2-(Pyrazol-1-yl)-4-methylquinoline (**4a**).

A mixture of 2-hydrazino-4-methylquinoline (**5**) (6 mmoles) and acetyl malonaldehyde bis(dimethylacetal) (6 mmoles) in ethanol containing a few drops of concentrated HCl was heated under reflux for 3 hours. After complete evaporation of solvent, the residue was extracted with chloroform (3 x 20 ml) and dried over magnesium sulfate. Excess of chloroform was distilled off to yield a gummy mass (yield 64%) which was used without further purification for nmr studies.

2-(3- and 5-Methylpyrazol-1-yl)-4-methylquinolines **4b** and **4f**.

A mixture of 2-hydrazino-4-methylquinoline (**5**) (2 mmoles) and acetyl acetaldehyde dimethyl acetal (2 mmoles) in ethanol containing a few drops of concentrated HCl was heated under reflux for 3 hours. On cooling, a solid separated out, which was found to be a mixture of two compounds (tlc and ^{1}H nmr). Column chromatography over a silica-gel (60-120 mesh) column using light petroleum (60-80°) afforded **4f**, mp 75-76°, yield 45%.

Anal. Calcd. for $C_{14}H_{13}N_3$: N, 18.83. Found: N, 18.65.

Further elution of the column afforded **4b**, mp 65-66°, yield 23%.

Anal. Calcd. for $C_{14}H_{13}N_3$: N, 18.83. Found: N, 18.79.

2-(5-Alkylpyrazol-1-yl)-4-methylquinolines 4g-4i.

A mixture of 2-hydrazino-4-methylquinoline (**5**) (3 mmoles) and sodium salt of an appropriate β-ketoaldehyde (*vide infra*) (3 mmoles) was stirred at room temperature in the presence of a few drops of concentrated HCl for 30 minutes and then refluxed for 2 hours. The solvent was evaporated and the residue was extracted with chloroform (3 x 20 ml) and dried over magnesium sulfate. Removal of chloroform gave a gummy mass in each case which was purified by column chromatography using light petroleum (60-80°): ethyl acetate (5:1) to furnish **4g-4i**.

Compound **4g** had mp 58-59°, yield 37%.

Anal. Calcd. for $C_{15}H_{15}N_3$: N, 17.72. Found: N, 17.30.

Compound **4h** had mp 52-53°, yield 40%.

Anal. Calcd. for $C_{16}H_{17}N_3$: N, 16.73. Found: N, 16.27.

Compound **4i** had mp 73-74°, yield 58%.

Anal. Calcd. for $C_{17}H_{19}N_3$: N, 15.84. Found: N, 15.57.

3(5)-Alkylpyrazoles (R = ethyl, *iso*-propyl, *tert*-butyl).

A mixture of an appropriate ketone (169 mmoles) and ethyl formate (169 mmoles) was added dropwise to a slurry of sodium methoxide (175 mmoles) in anhydrous ether (150 ml) with constant stirring. The reaction mixture was heated under reflux for 4 hours, cooled and treated with hydrazine hydrate (169 mmoles) followed by acidification with concentrated sulfuric acid. The *p*H of the yellowish solution obtained was readjusted to neutral and the product was extracted with chloroform (3 x 20 ml). The combined extract was dried over magnesium sulfate and chloroform distilled off to afford the 3(5)-alkylpyrazoles which were subsequently used without further purification. The three of them are known compounds: 3(5)-ethylpyrazole [14], 3(5)-*iso*-propylpyrazole [15] and 3(5)-*tert*-butylpyrazole [16].

2-(3-Alkylpyrazol-1-yl)-4-methylquinolines 4c-4e.

A solution of the corresponding 3(5)-alkylpyrazole (5 mmoles) in anhydrous diglyme (30 ml) was stirred with sodium hydride (6 mmoles) at room temperature for 30 minutes, 2-Chloro-4-methylquinoline (**6**) (5 mmoles) was subsequently added and the reaction mixture was refluxed for 12 hours. After distilling the excess of diglyme, the residue was poured into cold water (100 ml) and extracted with chloroform (3 x 25 ml). The combined extract was dried over magnesium sulfate and chloroform was removed. The residue thus obtained in each case was purified by column chromatography using light petroleum (60-80°): ethyl acetate (10:1) to afford **4c-4e**. Compound **4c** had mp 95-96°, yield 30%.

Anal. Calcd. for $C_{15}H_{15}N_3$: N, 17.72. Found: N, 17.39.

Compound **4d** had mp 72-74°, yield 42%.

Anal. Calcd. for $C_{16}H_{17}N_3$: N, 16.73. Found: N, 16.46.

Compound **4e** had mp 73°, yield 55%.

Anal. Calcd. for $C_{17}H_{19}N_3$: N, 15.84. Found: N, 15.81.

During the synthesis of **4c** another component was isolated by repeated column chromatography in about 25% yield. The compound, mp 91-92° was characterized as 2-(3,4-dimethyl-pyrazol-1-yl)-4-methylquinoline by its ^{1}H nmr spectrum showing signals at δ 2.02 (s, 3H, C4'-CH$_3$), 2.23 (s, 3H, C3'-CH$_3$), 2.62 (s, 3H, C4-CH$_3$), 7.24-8.04 (m, 5H), 8.37 (s, 1H, C5'-H). The formation of this product can be rationalized assuming the β-ketoester to be a mixture of two compounds resulting from a Claisen condensation between 2-butanone and ethyl formate [17,18].

Anal. Cacld. for $C_{15}H_{15}N_3$: N, 17.72. Found: N, 17.04

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