^1H and ^{13}C NMR study of the pyrazolo[1,5-*a*]pyrimidine system

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The ^{13}C and ^1H NMR spectra of some pyrazolo[1,5-*a*]pyrimidine derivatives are discussed. All ^{13}C resonances were unambiguously assigned by means of both 2D experiments and gated decoupled spectra from which one-bond and long-range ^{13}C–^1H coupling constants were determined. The literature assignments for H-5 and H-7 in the parent system have been revised and a simple method for distinguishing between 5-methyl and 7-methyl compounds is suggested, based on the carbon chemical shift of the methyl group or on its fine structure in the ^1H NMR spectrum. Regioselective syntheses for all the reported methyl derivatives are also described.

STEFANO CHIMICHI, BARBARA COSIMELLI, FABRIZIO BRUNI et SILVIA SELLERI. Can J. Chem. **70**, 1093 (1992).

On discute des spectres RMN du ^1H et du ^{13}C de quelques dérivés pyrazolo[1,5-*a*]pyrimidine. On a attribué toutes les raies de spectres ^{13}C d'une façon non-ambiguë à l'aide d'expériences en 2D et de spectres découplés à connexion intermittente à partir desquels on a déterminé les constantes de couplage ^{13}C–^1H à travers une et plusieurs liaisons. On a révisé les attributions faites dans la littérature pour les H-5 et H-7 et on suggère une méthode simple pour distinguer les composés portant des méthyles en 5 ou en 7; elle est basée sur le déplacement chimique du carbone des groupes méthyles ou sur la structure fine dans les spectres RMN du ^1H. On décrit aussi des synthèses régiospécifiques pour tous les dérivés méthyles examinés.

[Traduit par la rédaction]

Introduction

As part of our continuing interest in hetero-condensed five-membered heterocycles (1–3), we recently reported a new synthetic pathway to pyrazolo[1,5-*a*]pyrimidines (4). During this work, we noticed the lack of carbon-13 NMR data for this class of compound, some members of which show interesting biological properties (5–7).

We report here a detailed ^{13}C and ^1H NMR study of some pyrazolo[1,5-*a*]pyrimidines, including the parent ring system, carried out by means of gated decoupled, hetero- and homonuclear correlation spectroscopy techniques. We also demonstrate that NMR spectroscopy can be valuable for distinguishing the isomeric 7-methyl and 5-methyl derivatives, this not being easily achieved by other common spectroscopic techniques.

Experimental

Chemicals

3(5)-Aminopyrazole and 4,4-dimethoxybutan-2-one (acetylacetaldehyde dimethyl acetal) are commercially available (Aldrich); 5-amino-3-phenylpyrazole and compounds **1**, **4**, **5**, and **8** were synthesized according to published procedures (8–12, respectively).

5-Methylpyrazolo[1,5-a]pyrimidine (2)

The procedure reported by Bajwa and Sykes (13) was modified by adding 4,4-dimethoxybutan-2-one (1.00 g, 7.6 mmol) to a solution of 3(5)-aminopyrazole (0.57 g, 6.9 mmol) in EtOH (3.5 mL). The solution was then refluxed for 30 min; removal of the solvent left a yellow solid (0.86 g, 94%) mainly consisting (90%, TLC and ^1H NMR spectrum) of compound **2**, together with a very small quantity of the 7-methyl isomer. An analytical sample (colorless plates) obtained by recrystallization from petroleum ether melted at 122–123°C (lit. (13) mp 122–124°C).

7-Methylpyrazolo[1,5-a]pyrimidine (3)

A solution of 3(5)-aminopyrazole (0.57 g, 6.9 mmol) in EtOH (3.5 mL) was added to a solution of the β-keto-acetal (1.00 g, 7.6 mmol) in concentrated HCl (0.3 mL). The solution was refluxed for 30 min and then poured into water (20 mL) and extracted exhaustively with diethyl ether. The ethereal extracts were washed with water (50 mL) and dried on Na_2SO_4. Evaporation to dryness left a yellow solid (0.66 g, 80%) containing the isomeric 7- and 5-methyl derivatives in the ratio 87:13. The mixture was resolved by flash chromatography with ethyl acetate/petroleum ether (bp 40–70°C) (1:1 v/v) as eluent; the faster band gave compound **3** (77%), mp 58–59°C (from petroleum ether) (lit. (13) mp 59–60°C). The second compound was easily recognized (TLC, ^1H NMR spectrum) as 5-methylpyrazolo[1,5-*a*]pyrimidine (**2**) (10%).

5-Methyl-1-phenylpyrazolo[1,5-a]pyrimidine (6)

Operating as for compound **2** employing 5-amino-3-phenylpyrazole, a pink solid (0.62 g, 95%) consisting mainly (96%, TLC and ^1H NMR spectrum) of compound **6** was obtained. An analytical sample (colorless plates) melted at 177–178°C (from ethyl acetate). Anal. calcd. for $C_{13}H_{11}N_3$: C 74.62, H 5.3, N 20.08; found: C 74.26, H 5.21, N 20.27.

7-Methyl-2-phenylpyrazolo[1,5-a]pyrimidine (7)

Operating as for compound **3** starting from 5-amino-3-phenylpyrazole, a yellow solid (0.61 g, 94%) containing the two isomeric 7- and 5-methyl derivatives (93:7) was obtained. Recrystallization from ethanol/water (1:1 v/v) afforded compound **7** as yellow needles, mp 93–94°C (lit. (14) mp 95–96°C).

Instruments

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Carbon-13 and proton NMR spectra were recorded on a Varian VXR-300 instrument in the Fourier transform mode. All carbon spectra were recorded in 10-mm o.d. tubes at 25 ± 0.5°C for 0.5 M solutions in $CDCl_3$, proton coupled spectra were obtained in the "gated decoupling" mode; proton spectra were recorded in 5-mm o.d. tubes at the same temperature. Chemical shifts are reported in ppm high frequency from

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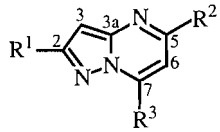

1 $R^1 = R^2 = R^3 = H$ **5** $R^1 = C_6H_5$, $R^2 = R^3 = H$

2 $R^1 = R^3 = H$, $R^2 = CH_3$ **6** $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = H$

3 $R^1 = R^2 = H$, $R^3 = CH_3$ **7** $R^1 = C_6H_5$, $R^2 = H$, $R^3 = CH_3$

4 $R^1 = H$, $R^2 = R^3 = CH_3$ **8** $R^1 = C_6H_5$, $R^2 = R^3 = CH_3$

SCHEME 1

TMS as secondary reference standard and coupling constants in Hz. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 230–400 mesh) were used for analytical TLC and for flash chromatographies, respectively. Solvents were removed under reduced pressure.

Results and discussion

The carbon chemical shifts of the examined compounds **1**–**8** (Scheme 1) are given in Table 1; spectra were analyzed on a first-order basis, the necessary assumptions being fulfilled. Coupling constants are assembled in Table 2; the assignments of carbon resonances (see below) are based on chemical shift arguments, on ^1J(CH) values, and on the fine splitting pattern caused by long-range couplings as well as on HETCOR spectra.

Chemical shift considerations did not always allow an unambiguous assignment; as regards compound **1**, apart from the singlet attributable to the quaternary carbon atom C-3a, the five methine ring carbons appear as doublets with further long-range couplings. The signals at lower frequencies (δ 96.86 and 107.66) are easily attributed to C-3 and C-6, respectively, because the former appears as a doublet of doublets ($^2J_{C3-H2}$ = 9.7 Hz) whereas the latter is a doublet of doublets of doublets due to the long-range couplings both to H-5 and H-7 ($^2J_{C6-H5}$ = 9.9 Hz and $^2J_{C6-H7}$ = 3.0 Hz). Assignment of C-2, C-5, and C-7 resonances is more difficult, their chemical shifts being very close, and was achieved on the following basis.

First, we attempted to assign all the proton resonances of compound **1** (Table 3) by a COSY-90 experiment, which would then be useful in rationalizing the heteronuclear correlation (HETCOR) spectrum. Unfortunately, the COSY spectrum, besides confirming the assignment of H-3 and H-6, allowed us only to attribute the signal at δ 8.166 to H-2; as regards H-7 and H-5 an unambiguous assignment was not attained. Moreover, the HETCOR spectrum shows that the most deshielded carbon atom is not connected with the most deshielded proton but with the signal at δ 8.461; this finding, together with chemical shifts considerations and the fine splitting pattern, suggested that the highest frequency signal in the ^{1}H NMR spectrum should be attributed to H-7 instead of H-5, contrary to the report of Lynch *et al.* (9). To reach a definitive assignment, we synthesized the methyl derivatives **2**, **6** and **3**, **7**. As for the preparation of these compounds, a synthetic pathway leading to a mixture of compounds **2** and **3** was reported in the literature (13) starting from 4,4-dimethoxybutan-2-one. A simple change in the experimental procedure (see Experimental) allowed us to make the synthesis highly regioselective also employing 3-

TABLE 1. ^{13}C NMR ($CDCl_3$, 75 MHz) chemical shifts (δ, ppm) of compounds **1**–**8**[a]

Compound	C-2	C-3	C3a	C-5	C-6	C-7	5-CH_3	7-CH_3	C-*ipso*	C-*ortho*	C-*meta*	C-*para*
1	145.04(dd)	96.86(dd)	148.54(m)	149.02(ddd)	107.66(ddd)	135.01(dm)	—	—	—	—	—	—
2	145.00(dd)	95.65(dd)	148.22[b](ddd)	158.93[c](ddq)	108.75[d](ddq)	134.41(dd)	24.79(qd)	—	—	—	—	—
3	144.34(dd)	96.93(dd)	148.82[b](ddd)	148.57(dd)	107.40(ddq)	146.04(m)	—	17.22(qd)	—	—	—	—
4	144.29(dd)	95.71(dd)	148.52[c](dd)	158.32(qd)	108.35[f](dqq)	145.16(qd)	24.59(qd)	17.04(qd)	—	—	—	—
5	156.03[g](dt)	93.28(d)	149.39(ddd)	148.75(ddd)	107.34(ddd)	134.37(ddd)	—	—	131.33	128.48	126.21	128.74
6	156.35[g](dt)	92.55(d)	149.37(dd)	159.01[c](ddq)	108.73[d](ddq)	134.17(dd)	24.82(qd)	—	132.80	128.77	126.44	128.93
7	155.68[g](dt)	93.65(d)	149.98(dd)	148.57(dd)	107.40(ddq)	146.03[e](ddq)	—	17.24(qd)	133.05	128.75	126.60	128.89
8	155.55[g](dt)	92.51(d)	149.66(d)	158.30(qd)	108.29[f](dqq)	145.17(qd)	24.60(qd)	17.04(qd)	133.22	128.70	126.51	128.73

[a] Multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).
[b] Appears as doublet of triplets.
[c] Appears as quintet of doublets.
[d] Appears as doublet of quintets.
[e] Appears as triplet.
[f] Appears as doublet of septuplets.
[g] Appears as quartet.

TABLE 2. Selected $^{n}J_{C,H}$ (Hz) of compounds **1–8**

Compound	C-2	C-3	C-3a	C-5	C-6	C-7	5-CH_3	7-CH_3
1	$^{1}J_{C\text{-}2,H\text{-}2}$ = 185.3 $^{2}J_{C\text{-}2,H\text{-}3}$ = 5.6	$^{1}J_{C\text{-}3,H\text{-}3}$ = 181.1 $^{2}J_{C\text{-}3,H\text{-}2}$ = 9.7	m[a]	$^{1}J_{C\text{-}5,H\text{-}5}$ = 183.7 $^{3}J_{C\text{-}5,H\text{-}7}$ = 6.2 $^{2}J_{C\text{-}5,H\text{-}6}$ = 2.6	$^{1}J_{C\text{-}6,H\text{-}6}$ = 171.1 $^{2}J_{C\text{-}6,H\text{-}5}$ = 9.9 $^{2}J_{C\text{-}6,H\text{-}7}$ = 3.0	$^{1}J_{C\text{-}7,H\text{-}7}$ = 186.3	—	—
2	$^{1}J_{C\text{-}2,H\text{-}2}$ = 184.6 $^{2}J_{C\text{-}2,H\text{-}3}$ = 5.6	$^{1}J_{C\text{-}3,H\text{-}3}$ = 180.4 $^{2}J_{C\text{-}3,H\text{-}2}$ = 9.7	$^{2}J_{C\text{-}3a,H\text{-}3}$ = 6.7 $^{3}J_{C\text{-}3a,H\text{-}2}$ = 6.7 $^{3}J_{C\text{-}3a,H\text{-}7}$ = 3.3	$^{2}J_{C\text{-}5,5CH_3}$ = 6.4 $^{3}J_{C\text{-}5,H\text{-}7}$ = 6.4 $^{2}J_{C\text{-}5,H\text{-}6}$ = 1.8	$^{1}J_{C\text{-}6,H\text{-}6}$ = 169.2 $^{2}J_{C\text{-}6,H\text{-}7}$ = 3.4 $^{3}J_{C\text{-}6,5CH_3}$ = 3.4	$^{1}J_{C\text{-}7,H\text{-}7}$ = 185.5 $^{2}J_{C\text{-}7,H\text{-}6}$ = 3.0	$^{1}J_{5CH_3}$ = 127.8 $^{3}J_{5CH_3,H\text{-}6}$ = 1.7	—
3	$^{1}J_{C\text{-}2,H\text{-}2}$ = 184.8 $^{2}J_{C\text{-}2,H\text{-}3}$ = 5.6	$^{1}J_{C\text{-}3,H\text{-}3}$ = 180.5 $^{2}J_{C\text{-}3,H\text{-}2}$ = 9.8	$^{3}J_{C\text{-}3a,H\text{-}5}$ = 13.9 $^{2}J_{C\text{-}3a,H\text{-}3}$ = 6.9 $^{3}J_{C\text{-}3a,H\text{-}2}$ = 6.9	$^{1}J_{C\text{-}5,H\text{-}5}$ = 181.8 $^{2}J_{C\text{-}5,H\text{-}6}$ = 2.2	$^{1}J_{C\text{-}6,H\text{-}6}$ = 168.4 $^{2}J_{C\text{-}6,H\text{-}5}$ = 9.6 $^{3}J_{C\text{-}6,7CH_3}$ = 4.6	m[a]	—	$^{1}J_{7CH_3}$ = 130.5 $^{3}J_{7CH_3,H\text{-}6}$ = 3.5
4	$^{1}J_{C\text{-}2,H\text{-}2}$ = 184.2 $^{2}J_{C\text{-}2,H\text{-}3}$ = 5.6	$^{1}J_{C\text{-}3,H\text{-}3}$ = 179.9 $^{2}J_{C\text{-}3,H\text{-}2}$ = 9.9	$^{2}J_{C\text{-}3a,H\text{-}3}$ = 6.9 $^{3}J_{C\text{-}3a,H\text{-}2}$ = 6.9	$^{2}J_{C\text{-}5,5CH_3}$ = 7.0 $^{2}J_{C\text{-}5,H\text{-}6}$ = 2.0	$^{1}J_{C\text{-}6,H\text{-}6}$ = 166.6 $^{3}J_{C\text{-}6,5CH_3}$ = 4.0 $^{3}J_{C\text{-}6,7CH_3}$ = 4.0	$^{2}J_{C\text{-}7,7CH_3}$ = 6.3 $^{2}J_{C\text{-}7,H\text{-}6}$ = 3.0	$^{1}J_{5CH_3}$ = 127.6 $^{3}J_{5CH_3,H\text{-}6}$ = 1.8	$^{1}J_{7CH_3}$ = 130.4 $^{3}J_{7CH_3,H\text{-}6}$ = 3.8
5	$^{2}J_{C\text{-}2,H\text{-}3}$ = 4.5 $^{3}J_{C\text{-}2,H\text{-}ortho}$ = 4.5	$^{1}J_{C\text{-}3,H\text{-}3}$ = 179.4	$^{3}J_{C\text{-}3a,H\text{-}5}$ = 13.7 $^{2}J_{C\text{-}3a,H\text{-}3}$ = 6.7 $^{3}J_{C\text{-}3a,H\text{-}7}$ = 3.4	$^{1}J_{C\text{-}5,H\text{-}5}$ = 183.6 $^{3}J_{C\text{-}5,H\text{-}7}$ = 6.2 $^{2}J_{C\text{-}5,H\text{-}6}$ = 2.6	$^{1}J_{C\text{-}6,H\text{-}6}$ = 171.1 $^{2}J_{C\text{-}6,H\text{-}5}$ = 9.9 $^{2}J_{C\text{-}6,H\text{-}7}$ = 3.0	$^{1}J_{C\text{-}7,H\text{-}7}$ = 186.0 $^{3}J_{C\text{-}7,H\text{-}5}$ = 6.4 $^{2}J_{C\text{-}7,H\text{-}6}$ = 3.6	—	—
6	$^{2}J_{C\text{-}2,H\text{-}3}$ = 4.0 $^{3}J_{C\text{-}2,H\text{-}ortho}$ = 4.0	$^{1}J_{C\text{-}3,H\text{-}3}$ = 178.8	$^{2}J_{C\text{-}3a,H\text{-}3}$ = 6.5 $^{3}J_{C\text{-}3a,H\text{-}7}$ = 3.2	$^{2}J_{C\text{-}5,5CH_3}$ = 6.4 $^{3}J_{C\text{-}5,H\text{-}7}$ = 6.4 $^{2}J_{C\text{-}5,H\text{-}6}$ = 2.1	$^{1}J_{C\text{-}6,H\text{-}6}$ = 169.1 $^{2}J_{C\text{-}6,H\text{-}7}$ = 3.4 $^{3}J_{C\text{-}6,5CH_3}$ = 3.4	$^{1}J_{C\text{-}7,H\text{-}7}$ = 185.3 $^{2}J_{C\text{-}7,H\text{-}6}$ = 3.3	$^{1}J_{5CH_3}$ = 127.8 $^{3}J_{5CH_3,H\text{-}6}$ = 1.7	—
7	$^{2}J_{C\text{-}2,H\text{-}3}$ = 4.2 $^{3}J_{C\text{-}2,H\text{-}ortho}$ = 4.2	$^{1}J_{C\text{-}3,H\text{-}3}$ = 178.8	$^{3}J_{C\text{-}3a,H\text{-}5}$ = 13.7 $^{2}J_{C\text{-}3a,H\text{-}3}$ = 6.7	$^{1}J_{C\text{-}5,H\text{-}5}$ = 181.7 $^{2}J_{C\text{-}5,H\text{-}6}$ = 2.6	$^{1}J_{C\text{-}6,H\text{-}6}$ = 168.5 $^{2}J_{C\text{-}6,H\text{-}5}$ = 9.5 $^{3}J_{C\text{-}6,7CH_3}$ = 4.6	$^{2}J_{C\text{-}7,7CH_3}$ = 6.5 $^{3}J_{C\text{-}7,H\text{-}5}$ = 6.5 $^{2}J_{C\text{-}7,H\text{-}6}$ = 3.1	—	$^{1}J_{7CH_3}$ = 130.6 $^{3}J_{7CH_3,H\text{-}6}$ = 3.6
8	$^{2}J_{C\text{-}2,H\text{-}3}$ = 4.0 $^{3}J_{C\text{-}2,H\text{-}ortho}$ = 4.0	$^{1}J_{C\text{-}3,H\text{-}3}$ = 177.9	$^{2}J_{C\text{-}3a,H\text{-}3}$ = 6.6	$^{2}J_{C\text{-}5,5CH_3}$ = 6.4 $^{2}J_{C\text{-}5,H\text{-}6}$ = 2.1	$^{1}J_{C\text{-}6,H\text{-}6}$ = 166.5 $^{3}J_{C\text{-}6,5CH_3}$ = 4.0 $^{3}J_{C\text{-}6,7CH_3}$ = 4.0	$^{2}J_{C\text{-}7,7CH_3}$ = 6.4 $^{2}J_{C\text{-}7,H\text{-}6}$ = 3.0	$^{1}J_{5CH_3}$ = 127.6 $^{3}J_{5CH_3,H\text{-}6}$ = 1.8	$^{1}J_{7CH_3}$ = 130.5 $^{3}J_{7CH_3,H\text{-}6}$ = 3.8

[a]Not resolved.

TABLE 3. Selected ^{1}H NMR ($CDCl_3$, 300 MHz) chemical shifts (δ, ppm) of compounds **1–8**[a]

Compound	H-2	H-3	H-5	H-6	H-7	5-CH_3	7-CH_3
1	8.17(d,$J_{3,2}$2.2)	6.69(dd,$J_{3,2}$2.2,$J_{3,7}$0.9)	8.46(dd,$J_{5,6}$4.0,$J_{5,7}$1.8)	6.79(dd,$J_{6,7}$7.0,$J_{6,5}$4.0)	8.67(ddd,$J_{7,6}$7.0,$J_{7,5}$1.8,$J_{7,3}$0.9)	—	—
2	8.06(dd,$J_{2,3}$2.4,$J_{2,7}$0.7)	6.55(dd,$J_{3,2}$2.4,$J_{3,7}$0.9)	—	6.67(d,$J_{6,7}$7.2)	8.53(ddd,$J_{7,6}$7.2,$J_{7,3}$0.9,$J_{7,2}$0.7)	2.60(s)	—
3	8.14(d,$J_{2,3}$2.4)	6.71(d,$J_{3,2}$2.4)	8.37(d,$J_{5,6}$4.1)	6.68(dq,$J_{6,5}$4.1,$J_{6,7CH_3}$0.9)	—	—	2.79(d,$J_{7CH_3,6}$0.9)
4	8.07(d,$J_{2,3}$2.4)	6.56(d,$J_{3,2}$2.4)	—	6.55(q,$J_{6,7CH_3}$0.9)	—	2.55(s)	2.73(d,$J_{7CH_3,6}$0.9)
5	—	7.00(d,$J_{3,7}$0.9)	8.46(dd,$J_{5,6}$4.1,$J_{5,7}$1.8)	6.79(dd,$J_{6,7}$7.0,$J_{6,5}$4.1)	8.68(ddd,$J_{7,6}$7.0,$J_{7,5}$1.8,$J_{7,3}$0.9)	—	—
6	—	6.84(d,$J_{3,7}$0.8)	—	6.65(d,$J_{6,7}$7.1)	8.53(dd,$J_{7,6}$7.1,$J_{7,3}$0.8)	2.60(s)	—
7	—	7.00(s)	8.36(d,$J_{5,6}$4.2)	6.67(dq,$J_{6,5}$4.2,$J_{6,7CH_3}$0.9)	—	—	2.85(d,$J_{7CH_3,6}$0.9)
8	—	6.85(s)	—	6.52(q,$J_{6,7CH_3}$0.9)	—	2.55(s)	2.77(d,$J_{7CH_3,6}$0.9)

[a]Multiplicity (s = singlet, d = doublet, q = quartet), $J_{H,H}$ (Hz).

TABLE 4. Substituent coupling constants (CH_3-SCC) for the pyrazolo[1,5-*a*]pyrimidines (Hz)

Compound	(5,6)[a]	(5,7)	(7,5)	(7,6)
2	−1.9	−0.8	—	—
3	—	—	−1.9	−2.7
6	−2.0	−0.7	—	—
7	—	—	−1.9	−2.6

[a]The numbering system (*m*,*n*) is referred to the pyrazolo[1,5-*a*]pyrimidine ring.

phenyl-5-aminopyrazole as starting material, thus obtaining the requisite 5- (compounds **2** and **6**) and 7-methyl derivatives (**3** and **7**). The regioisomers can be easily distinguished on the basis of the carbon chemical shift of the methyl group without a detailed analysis of the other spectral data. This substituent exhibits a diagnostic low-frequency shift (δ 24.8–24.6 vs. 17.2–17.0 ppm, respectively) on going from position 5 to 7. Moreover, as regards the proton spectrum, the methyl group in position 5 does not show coupling to H-6; on the contrary, a small coupling of 0.9 Hz between 7-CH_3 and H-6 is always present in the spectra of derivatives **3**, **4** and **7**, **8** (see Table 3). Because the C-5 and C-7 resonances are easily recognizable in the model compounds **3**, **4** and **7**, **8**, the attribution of signals for the corresponding atoms in compound **1** becomes straightforward. Once the carbon resonances have been established, the HETCOR spectrum allows an unambiguous assignment of H-5 and H-7 signals, thus showing that the previously reported one (9) must be reversed.

Comparison of ^1J(CH) values for pyrazolo[1,5-*a*]pyrimidines and pyrimidine (15) shows that the pyrazole ring fusion is responsible for an increase in all one-bond coupling constants with respect to pyrimidine, thus confirming the electron-withdrawing effect of the fused five-membered ring (1, 2). The methyl-substituted pyrazolo[1,5-*a*]pyrimidines show, as recently reported for other heterocycles (15, 16), additivity of substituent effects upon ^1J(CH). The substituent coupling constant (SCC) for the methyl group in the pyrazolo[1,5-*a*]pyrimidines (Table 4) is defined as the change that occurs in the value of ^1J(CH) at C-*n* upon substitution at a pyrimidine ring carbon, C-*m*($m \neq n$), by a methyl group. The ^1J(CH) values observed for the dimethyl derivatives **4** and **8** agree well with those calculated by using the CH_3-SCC values (166.5 vs. 166.6 Hz and 166.5 vs. 166.5 Hz, respectively).

Finally, it is interesting to note that the general rules outlined for other heterocyclic compounds (1, 17) hold for this ring system too. For example, ^2J(C-β,H-α), in which the coupled proton is geminal to an sp^2 nitrogen atom, and ^3J(CH) through an heteroatom are larger in comparison with other geminal or vicinal couplings, respectively, as well as ^3J(C, CH_3) being smaller than ^2J(C, CH_3) (15).

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