Research in the Azole Series. **103** [1]. Synthesis and ^{13}C NMR Study of Pyrazole-4-carboxaldehydes

Aurea Echevarría, José Elguero* and Wim Meutermans

Instituto de Química Médica, CSIC, Juan de la Cierva, 3,
E-28006 Madrid, Spain

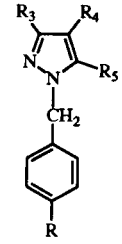
Received February 12, 1993

Ten new pyrazoles have been prepared and their ^{13}C nmr chemical shifts compared with those of twelve other pyrazoles, some of them prepared purposely for this study. The chemical shifts are discussed statistically assuming that they are additive. A formyl group in the position 4 of the pyrazole ring produces a large effect on carbon C_4 (SCS = 17.3 ppm) and medium effects on carbons C_3 (SCS = 1.9 ppm) and C_5 (SCS = 3.8 ppm). The azines derived from pyrazole-4-carboxaldehydes are of the *E,E*-configuration.

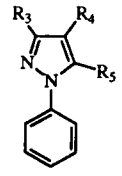
J. Heterocyclic Chem., **30**, 957 (1993).

Our interest in the synthesis of meso-substituted tetrapyrazolylporphyrines [2] led us to the synthesis and characterization by ^{13}C nmr spectroscopy of pyrazole-4-carboxaldehydes (4-formylpyrazoles), the starting materials for the synthesis of these porphyrines. These compounds, are usually prepared by formylation of 4-H pyrazoles using the Vilsmeier-Haack procedure [3-13], when the starting material is a pyrazolin-5-one the reaction results in a 4-formyl-5-chloro derivative [14,15], other procedures involve the use of triformylmethane [16], the reduction of esters [17] and the oxidation of the corresponding carbinols [18] (the parent compound has been prepared by these three last routes [16-18]).

In this paper we will describe three families of pyrazoles, *N*-benzyl, *N*-*p*-methoxybenzyl and *N*-phenyl. This second substituent was selected to have a group on the nitrogen which could be easily removed [19]. Some typical derivatives of pyrazole-4-carboxaldehydes have been prepared: imines [20], hydrazones [9,16,20], azines [16,21], oximes [7,20] and thioaldehydes [15]. Becher, very active in this field, has also described a rearrangement of 5-chloropyrazole-4-carboxaldehydes [13].



1-14



15-22

The *p*-methoxybenzylpyrazoles (see Table 1 for substituents) **7**, **8** and **9** were prepared in good yields from the corresponding NH-pyrazoles and *p*-methoxybenzyl chloride

Table 1

Chemical Shifts Values of *N*-(4-*R*-Benzyl) and *N*-Phenylpyraloles (in deuteriochloroform: δ, ppm)

Compound	R_3	R_4	R_5	R	C-3	C-4	C-5	CH_2	C-1'	C-2',6'	C3',5'	C-4'	R_3	R_4	R_5	R
1	H	H	H	H	139.4	105.9	129.1	55.8	136.9	127.7	128.8	128.0	–	–	–	–
2	CH_3	H	H	H	148.2	105.1	129.6	55.1	136.5	127.1	128.3	127.4	13.2	–	–	–
3	H	H	CH_3	H	138.3	105.6	138.1	52.7	136.5	126.1	128.1	126.9	–	–	–	–
4 [a,b]	H	CHO	H	H	140.0	124.0	134.6	55.2	136.3	127.7	128.5	127.7	–	184.5	–	–
5	CH_3	CHO	H	H	151.0	124.5	134.6	56.0	134.6	127.9	128.9	128.4	12.7	184.1	–	–
6	H	$(CH=N)_2$	H	H	139.7	118.5	129.7	56.3	135.5	127.8	128.8	127.8	–	153.2	–	–
7 [a]	H	H	H	OCH_3	139.1	105.6	130.0	54.4	129.9	129.4	114.1	159.0	–	–	–	55.4
8 [a]	CH_3	H	H	OCH_3	147.2	104.8	130.3	54.0	129.7	129.0	113.8	158.8	13.2	–	–	54.9
9 [a]	H	H	CH_3	OCH_3	137.7	105.3	137.7	51.5	129.5	128.2	113.8	158.6	–	–	10.5	54.9
10	H	CHO	H	OCH_3	140.6	126.5	132.3	55.9	129.5	129.6	114.3	159.7	–	183.9	–	55.1
11	CH_3	CHO	H	OCH_3	150.7	121.4	134.1	55.5	129.5	129.5	114.2	159.6	12.6	184.0	–	55.0
12	H	CHO	CH_3	OCH_3	141.3	121.1	141.3	52.3	129.4	128.3	114.1	159.2	–	184.5	10.2	55.0
13 [a]	CH_3	$(CH=N)_2$	H	OCH_3	147.8	114.9	131.3	54.3	131.1	129.1	113.7	158.8	12.8	152.8	–	54.8
14 [a]	H	$(CH=N)_2$	CH_3	OCH_3	138.1	114.9	139.3	51.7	128.4	128.2	113.7	158.7	9.8	147.8	–	54.8
15 [c]	H	H	H	C_6H_5	141.1	107.6	126.8	–	140.5	119.4	129.5	126.5	–	–	–	–
16	CH_3	H	H	C_6H_5	150.7	107.6	127.4	–	139.9	118.6	129.1	126.0	13.7	–	–	–
17	H	H	CH_3	C_6H_5	139.4	106.3	135.3	–	N.o.	124.5	128.5	127.5	–	–	14.6	–
18	H	CHO	H	C_6H_5	141.9	125.5	130.2	–	138.9	119.4	129.4	127.6	–	183.8	–	–
19 [a]	CH_3	CHO	H	C_6H_5	151.8	122.9	131.7	–	139.0	119.4	129.6	127.5	12.9	184.2	–	–
20 [a]	CH_3	CHO	CH_3	C_6H_5	150.2	118.5	138.0	–	N.o.	125.1	129.2	128.4	12.5	185.7	10.7	–
21 [a]	CH_3	CHO	Cl	C_6H_5	150.8	116.8	132.6	–	136.5	125.3	129.3	129.3	13.2	184.0	–	–
22	CH_3	$(CH=N)_2$	H	C_6H_5	151.0	117.6	127.4	–	139.5	119.1	129.5	126.8	13.0	153.5	–	–

[a] In DMSO-d_6. [b] These values are those of Heinish [11,20]. [c] Compounds **16-23** are *N*-phenyl derivatives. N.o. Not observed.

in the presence of a catalytic amount of tetrabutylammonium hydrogensulfate. The formyl derivatives **4,5**, **10-12**, **18-21**, were obtained by treating the corresponding pyrazoles with dry dimethylformamide and phosphorus oxychloride at reflux, the yields were moderate to good (40-80%). Symmetrical azines, **6**, **13**, **14** and **22**, were obtained by conventional methods [21], the crystalline products are pure *E,E*-isomers, as all other aldazines derived from aromatic aldehydes and, in particular, like **22** [21].

Compounds **5**, **6-14** are new compounds, the other compounds were already known but their study by ^{13}C nmr spectroscopy was necessary for comparative purposes. The chemical shifts of the following compounds of Table 1 were taken from the literature: **1** [22], **4** [11], **15**, **16**, **17** [22].

There is a large amount of information concerning ^{13}C nmr spectroscopy of pyrazoles (a recent review reports more than 1100 of such compounds [22]) thus there is generally no problem to assign the different signals reported in Table 1. Instead of discussing the SCS (substituent chemical shifts) of Table 1 in a conventional way we have preferred a statistical discussion. If the SCS are additive, *i.e.*, if they depend only on the nature and the position of the substituent, it is possible to describe 21 compounds of Table 1 in a matricial way (compound **21** being the only representative of a chloro substituted pyrazole, has been excluded). Taking as reference compound 1-phenylpyrazole (**15**) (the conclusions are independent of the chosen reference), the absence-presence matrix of Table 2 has been built.

Table 2

Matrix of the Substituent Effects on the Three Pyrazole Carbons

Compound	X_1	X_2	X_3	X_4	X_5	X_6
1	1	0	0	0	0	0
2	1	0	1	0	0	0
3	1	0	0	0	0	1
4	1	0	0	1	0	0
5	1	0	1	1	0	0
6	1	0	0	0	1	0
7	0	1	0	0	0	0
8	0	1	1	0	0	0
9	0	1	0	0	0	1
10	0	1	0	1	0	0
11	0	1	1	1	0	0
12	0	1	0	1	0	1
13	0	1	1	0	1	0
14	0	1	0	0	1	1
15	0	0	0	0	0	0
16	0	0	1	0	0	0
17	0	0	0	0	0	1
18	0	0	0	1	0	0
19	0	0	1	1	0	0
20	0	0	1	1	0	1
22	0	0	1	0	1	0

X_1: *N*-benzyl, X_2: *N*-*p*-methyoxybenzyl, X_3: 3-methyl; X_4: 4-formyl; X_5: 4-aldazine, X_6: 5-methyl.

Carbon C_3:
Constant: 140.7 ppm, X_1 = -1.5 ppm, X_2 = -1.8 ppm, X_3 = 9.3 ppm, X_4 = 1.9 ppm, X_5 = 0.4 ppm, X_6 -0.9 ppm; r^2 = 0.986, standard deviation = 0.8 ppm.

Carbon C_4:
Constant: 108.5 ppm, X_1 = -0.9 ppm, X_2 = -1.4 ppm, X_3 = -2.3 ppm, X_4 = 17.3 ppm, X_5 = 10.8 ppm, X_6 = -2.9 ppm; r^2 = 0.981, standard deviation = 1.4 ppm.

Carbon C_5:
Constant: 126.5 ppm, X_1 = 3.2 ppm, X_2 = 3.2 ppm, X_3 = 0.6 ppm, X_4 = 3.8 ppm, X_5 = 0.7 ppm, X_6 = 8.1 ppm; r^2 = 0.980, standard deviation = 0.8 ppm.

The constant terms are near the experimental values for compound **15** (X_i(i = 1,6) = 0). The effects of a formyl group on carbons C_3 (1.9 ppm), C_4 (17.3 ppm) and C_5 (3.8 ppm) are close to those described by Heinisch and Holzer [11] for the pair **1-4** (1.2, 18.7 and 4.8 ppm). Substituents on the nitrogen (X_1, X_2) affect essentially C_5; substituents on the carbon affect mainly the *ipso* carbon (X_3 on C_3, X_4 and X_5 on C_4 and X_6 on C_5) and less the adjacent carbon (X_3 on C_4, X_4 on C_3 and C_5 and X_6 on C_4), otherwise they are quite similar for the same substituent (methyl *ipso* effects: 9.3 and 8.1 ppm, methyl *ortho* effects: −2.3 and −2.9 ppm). The azine group effects are smaller than those of the formyl group being the former less electron-withdrawing. The signal of C_5 in 1-phenyl-5-methylpyrazole **17** appears at 138.3 ppm [22], a value of 134.6 ppm would be more consistent with the model we have used; in this case, perhaps the additivity is not followed due to an steric interaction between the 1-phenyl and the 5-methyl groups.

EXPERIMENTAL

Melting points were determined with a Reichert Jung microscope apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Varian Gemini 200 MHz spectrometer. Reagents and solvents were purchased from common commercial suppliers and were used without further purification. Yields were not optimized. 1-Benzylpyrazole (**1**), 1-benzyl-3-methylpyrazole (**2**) and 1-benzyl-5-methylpyrazole (**3**), were prepared according to the method previously described in the literature [23]. 1-Phenylpyrazole (**15**), 1-phenyl-3-methylpyrazole (**16**) and 1-phenyl-5-methylpyrazole (**17**), are commercially available. Finally, aldehyde **21** was a gift from Professor J. Becher [13].

General Procedure for the Preparation of 1-[*p*-Methoxybenzyl]-pyrazoles.

A mixture of the appropriate pyrazole (25 mmoles), potassium carbonate (2.76 g, 20 mmoles), powdered potassium hydroxide (1.12 g, 20 mmoles), tetrabutylammonium hydrogensulfate (0.1 g, 3 mmoles), *p*-methoxybenzyl chloride (4.05 ml, 30 mmoles) and toluene (200 ml) was refluxed for 20 hours. Progress of the reaction was monitored by tlc plates. The precipitate was filtered, washed with toluene and the filtrate dried over sodium sulfate, concentrated *in vacuo* and purified by fractional distillation to give the product **7** and the 50:50 mixture of isomers **8** and **9**, which have not been separated (see Table 3).

Table 3

Physical and Analytical Data of Compounds **4-8, 10, 11, 13, 14, 18, 19, 20, 21**

Product No.	R_3	R_4	R_5	N-R	Yield (%)	Bp (°C) (0.05 mmH)	Mp (°C)	Molecular Formula	Elemental Analysis (Calcd. % Found %) C	H	N
4	H	CHO	H	$CH_2C_6H_5$	55	115 [a]	-	$C_{11}H_{10}N_2O$ (186.23)	70.95 70.92	5.41 5.51	15.05 15.23
5	CH_3	CHO	H	$CH_2C_6H_5$	79	135-140	-	$C_{12}H_{12}N_2O$ (200.25)	71.98 72.07	6.04 5.97	13.99 14.23
6 [b]	H	$(CH=N)_2$	H	$CH_2C_6H_5$	50	-	129-132	$C_{22}H_{20}N_6$ (368.48)	71.71 71.85	5.47 5.30	22.81 22.48
7 [c]	H	H	H	*p*-$OMeC_6H_4$	80	98-108	-	$C_{11}H_{12}N_2O$ (188.24)	70.19 70.41	6.42 6.53	14.89 15.20
8 [d]	CH_3	H	H	*p*-$OMeC_6H_4$	50	110-115	-	$C_{12}H_{14}N_2O$ (202.26)	71.26 71.33	6.98 7.02	13.85 14.07
10 [e]	H	CHO	H	*p*-$OMeC_6H_4$	55	-	120	$C_{12}H_{12}N_2O_2$ (216.26)	66.64 66.24	5.60 5.87	12.96 13.02
11 [f]	CH_3	CHO	H	*p*-$OMeC_6H_4$	56	160-180 [g]	-	$C_{13}H_{14}N_2O_2$ (230.28)	67.81 67.81	6.13 6.25	12.17 11.98
13 [h]	CH_3	$(CH=N)_2$	H	*p*-$OMeC_6H_4$	25	-	147-150	$C_{26}H_{28}N_6O_2$ (456.60)	68.39 68.53	6.19 6.32	18.41 18.44
18	H	CHO	H	C_6H_5	51	-	120-121	$C_{10}H_8N_2O$ (172.19)	69.75 70.01	4.68 4.51	16.27 16.42
19	CH_3	CHO	H	C_6H_5	47	60-61 [i]	-	$C_{11}H_{10}N_2O$ (186.22)	70.95 70.08	5.41 5.39	15.05 15.07
20	CH_3	CHO	CH_3	C_6H_5	42	128 [j]	-	$C_{12}H_{12}N_2O$ (200.25)	71.98 72.06	6.04 6.17	13.99 14.21
22	CH_3	$(CH=N)_2$	H	C_6H_5	20	-	166-168 [l]	$C_{22}H_{20}N_6$ (368.48)	71.71 71.94	5.47 5.35	22.81 22.52

[a] [11]. [b] Mass spectrum for M^+: Calcd. m/z = 368.48, Found: m/z = 368.5. [c] Mass spectrum for M^+: Calcd. m/z = 188.24, found: m/z = 188.2. [d] This product corresponds to a mixture of isomers 8 and 9. [e] Mass spectrum for M^+: Calcd. m/z = 216.26. Found: m/z = 216.2. [f] This product corresponds to a mixture of isomers 11 and 12. [g] Distilled in a Kugelrhor. [h] This product corresponds to a mixture of isomers 13 and 14. [i] [6]. [j] [3]. [l] Lit mp = 160-162° [21].

General Procedure for the Preparation of 4-Formylpyrazoles.

Phosphorus oxychloride (39.8 g, 26 mmoles) was added dropwise slowly to a stirred solution of freshly distilled dimethylformamide (23 ml, 30 mmoles) containing the appropriate *N*-substituted pyrazoles (30 mmoles) at 90-100°. After complete addition the reaction mixture was stirred for another 3 hours under the same conditions. The reaction mixture was cooled and ice-water added. The *p*H was adjusted to 4 with a diluted sodium hydroxide solution and then extracted with ether. The ethereal fraction was washed with hydrochloric acid (1 *N*), with a diluted solution of sodium bicarbonate and then dried over sodium sulfate. After evaporation the residue was distilled under high vacuum to give the *N*-substituted pyrazole-4-carboxaldehydes (**4, 5, 10-12**). In the case of *N*-phenyl-substituted pyrazoles, after adjustment of the *p*H, the precipitate was filtered and purified by sublimation (**19**) or recrystallized with ethanol (**20**) (see Table 3). These compounds present a ν (C=O) band at 1670-1675 cm^{-1} in infrared (potassium bromide pellets).

General Procedure for the Preparation of Pyrazole-azines.

An equimolar quantity of the corresponding *N*-substituted pyrazole-4-carboxaldehyde was added to a very diluted ethanolic solution of equimolar quantities of hydrazine sulfate and sodium carbonate. The reaction mixture was stirred for 5 to 6 hours. The residue was filtered and the filtrate evaporated, cooled, and the crystalline products were isolated and recrystallized in ethanol. In this way azines **6, 13** and **22** were obtained (Table 3). Only compound **22** has been already described [21].

Acknowledgement.

A grant from the CNPQ of Brazil (A.E.) and a Special Action from CSIC are greatly acknowledged.

REFERENCES AND NOTES

[1] For part **102** see: R. M. Claramunt, P. Domiano, J. Elguero and J. L. Lavandera, *Bull. Soc. Chim. France*, 472 (1989).

[2] M. Bruix, J. Elguero and W. Meutermans, *J. Chem. Res.*, Short Communication, 370 (1992).

[3] I. L. Finar and G. H. Lord, *J. Chem. Soc.*, 3314 (1957).

[4] I. L. Finar and G. H. Lord, *J. Chem. Soc.*, 1819 (1959).

[5] J. D. Kendall and G. F. Duffin, British Patent 797,144 (1958); *Chem. Abstr.*, **53**, 4984e (1959).

[6] I. L. Finar and M. Manning, *J. Chem. Soc.*, 2733 (1961).

[7] M. A. Kira, M. O. Abdel-Rahman and K. Z. Gadalla, *Tetrahedron Letters*, 109 (1969).

[8] M. A. Kira, M. N. Aboul-Enein and M. I. Korkor, *J. Heterocyclic Chem.*, **7**, 25 (1970).

[9] P. Cohen-Fernandes and C. L. Habraken, *Rec. Trav. Chim. Pays Bas*, **91**, 1185 (1972).

[10] J. Becher, P. H. Olisen, N. A. Knudsen and H. Toftlund, *Sulfur Letters*, **4**, 175 (1986).

[11] G. Heinish and W. Holzer, *Heterocycles*, **27**, 2443 (1988).

[12] N. Malhotra, B. Fält-Hansen and J. Becher, *J. Heterocyclic Chem.*, **28**, 1837 (1991).

[13] J. Becher, P. L. Jørgensen, K. Pluta, N. J. Krake and B. Fält-Hansen, *J. Org. Chem.*, **57**, 2127 (1992).

[14] J. Becher, K. Pluta, N. J. Krake, K. Brøndum, N. J. Christensen and M. V. Vinader, *Synthesis*, 530 (1989).

[15] J. Becher, P. L. Jørgensen, H. Frydendhal and B. Fält-Hansen, *Synthesis*, 609 (1991).

[16] K. Takagi, A. Bajnati and M. Hubert-Habart, *J. Heterocyclic Chem.*, **27**, 1847 (1990).

[17] C. V. Greco and F. Pellegrini, *J. Chem. Soc., Perkin Trans. 1*, 720 (1972).

[18] J. Elguero, C. Marzin and M. E. Peek, *Bull. Soc. Chim. Belg.*, **84**, 499 (1975).

[19] M. Begtrup, *Bull. Soc. Chim. Belg.*, **97**, 573 (1988).

[20] G. Henish and W. Holzer, *Monatsch. Chem.*, **121**, 837 (1990).

[21] J. Elguero, R. Jacquier and C. Marzin, *Bull. Soc. Chim. France*, 713 (1968).

[22] 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).

[23] H. J. M. Dou, J. Elguero, M. Espada and P. Hassanaly, *An. Quim.*, **74**, 1137 (1978).