Pergamon

Tetrahedron, Vol. 53, No. 34, pp. 11645-11658, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00733-3

Synthesis and Molecular Structure of New O/N/O Ligands: Bis-Phenol-Pyridine and Bis-Phenol-Pyrazole

Artur M. S. Silva*, Lúcia M. P. M. Almeida and José A. S. Cavaleiro

Departament of Chemistry, Universiy of Aveiro, 3810 Aveiro (Portugal)

Concepción Foces-Foces* and Antonio L. Llamas-Saiz

Departamento de Cristalografía, Instituto de Química Física 'Rocasolano', CSIC, Serrano 119, E-28006 Madrid (Spain)

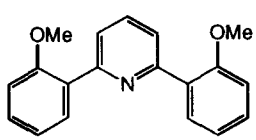
Christophe Fontenas, Nadine Jagerovic and José Elguero

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

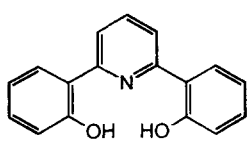
Abstract.— Two new heterocyclic ligands, 2,6-bis-(2'-hydroxyphenyl)pyridine **2** and 3,5-bis-(2'-hydroxyphenyl)pyrazole **4** have been prepared. The molecular structures of 2,6-bis-(2'-methoxyphenyl)pyridine **1**, the tetrafluoroborate salt of 2,6-bis-(2'-hydroxyphenyl)pyridine **3** (a monohydrate) and that of compound **4** have been determined by X-Ray analysis. In **1**, the phenyl rings are oriented so that the oxygen atoms of the methoxy groups are placed away from the nitrogen of the pyridine to overcome electronic repulsion. In salt **3**, intramolecular hydrogen bonds are found between the pyridinium proton and the hydroxyl atoms which are involved in strong O-H···O and O-H···F interactions. In addition, the water molecule participates in a bridging hydrogen bond network with the BF_4^-. The molecules in **4**, are also held together by hydrogen bonds where the hydroxyl groups act as both a donor and an acceptor and are responsible for the formation of chains.

INTRODUCTION

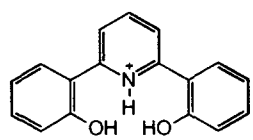
There is a continued interest in new polydentate ligands usually formed by a central heteroaromatic ring conveniently linked to one or two arms bearing heteroatoms (these arms can be heterocycles). For ligands N/N/N and S/N/S(the central position being that of a nitrogen heterocycle) there are many papers and even several reviews available.[1-7] In this paper we will devote our attention to much less common O/N/O ligands where the central position is occupied by a nitrogen heterocycle, either pyridine, compounds **1-3**, or pyrazole, compound **4**.



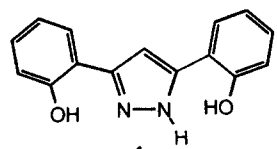
1



2

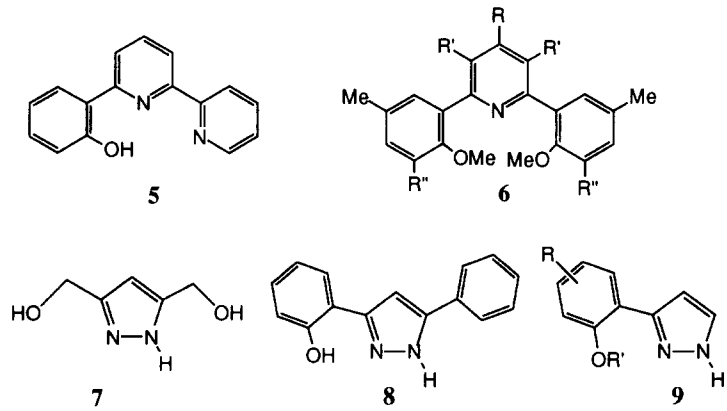


3



4

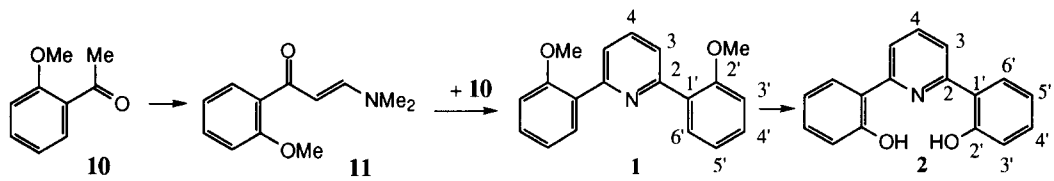
The closest related ligands are 6-(2'-hydroxyphenyl)-2,2'-bipyridine **5**,[8] the hemispherands **6** (always carrying several substituents),[9] 3,5-pyrazoledimethanol **7**,[10] **8**, the dehydroxy analogue of compound **4**,[11] and 3(5)-*o*-hydroxyphenylpyrazole **9** (R = R' = H)[12] and 3(5)-methoxyphenylpyrazoles **9** (R' = CH_3).[13]



Scheme 1

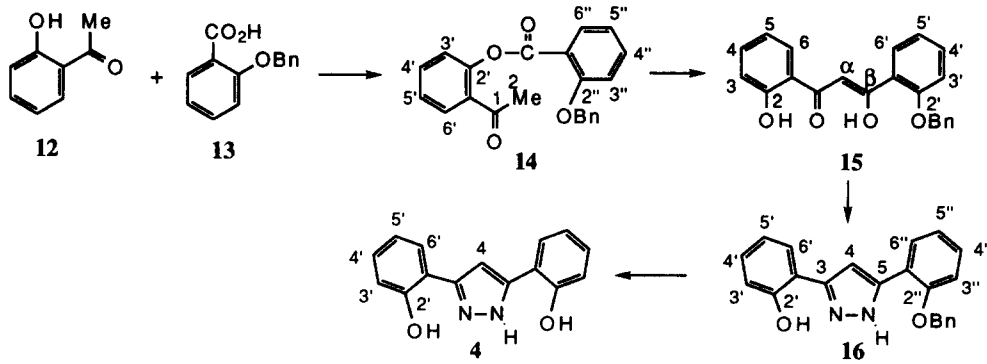
RESULTS AND DISCUSSION

Chemistry. Pyridine derivatives. Compounds **1** and **2** were prepared according to the procedure outlined in Scheme 2 with acceptable yields in every step. Demethylation of compound **1** to afford **2** was carried out by using pyridinium hydrochloride.[14] The tetrafluoroborate of pyridinium **3** was obtained from **2** and tetrafluoroboric acid in dichloromethane.



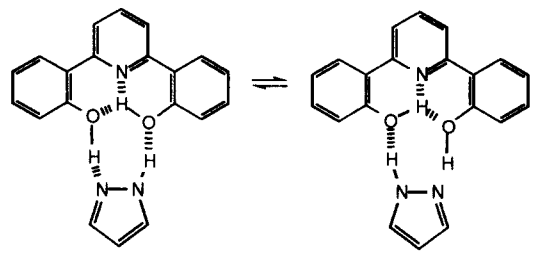
Scheme 2

Pyrazole derivatives. Compound **4** was prepared by the multi-step procedure represented in Scheme 3. First the chalcone **15** was prepared and then the semi-protected pyrazole **16** was obtained. For the debenzylation step, palladium and ammonium formate were used.



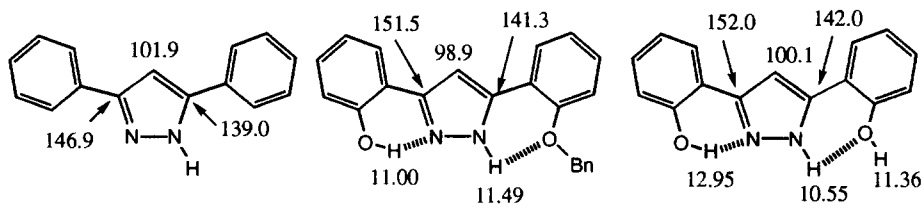
Scheme 3

NMR Spectroscopy. The pyridine derivatives **1** and **2** present usual NMR properties, consequently the data reported in the experimental part will not be commented. Experiments (^{1}H NMR) of mixing compound **2** and pyrazole (pyH) failed to demonstrate the existence of 1:1 complexes in solution, perhaps due to the fact that ligand **2** is not planar and does not present intramolecular O-H···N hydrogen bonds (see next section).



2,pzH 2,pzH

Owing to annular tautomerism (prototropic tautomerism involving only ring nitrogen atoms),[15] the NMR spectroscopy of pyrazoles **16** and **4** was studied in more detail. We have summarized in Scheme 4 the most relevant information (more details in the experimental section).



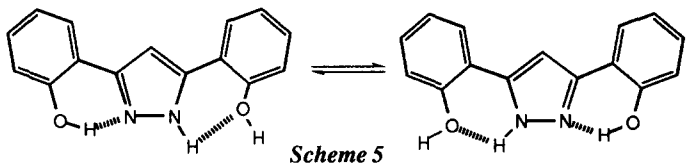
17 (Solid state CPMAS)

16 (Solution in CD_3COCD_3 at 293 K)

4 (Solution in CD_3COCD_3 at 223 K)

Scheme 4

In solution, 3,5-diphenylpyrazole **17** shows average signals due to rapid prototropy in the NMR time scale.[16] In the solid state, on the other hand, since there is no prototropy, the signals belonging to C-3 (146.9 ppm) and C-5 (139.0 ppm) are well apart ($\Delta\delta$ = 7.9 ppm). Compound **16** shows in solution at room temperature, both in ^1H and in ^{13}C NMR, signals corresponding to the tautomer represented in Scheme 4. The deshielding of N-H and O-H protons indicates intramolecular hydrogen bonds (in 3-*o*-hydroxyphenylpyrazoles, **9**, R' = H, the OH protons resonate at 10.93 ppm),[12] and the signals of pyrazole carbons are very different ($\Delta\delta$ = 10.2 ppm). The most interesting case is that of compound **4**. At room temperature (293 K) the three protons bonded to heteroatoms appear as a very broad signal at about 11 ppm, indicating that a degenerate tautomeric process is taking place (Scheme 5). Lowering the temperature results in the splitting of the broad signal into three signals (the assignment of Scheme 4 is only tentative).



Scheme 5

For the same reason, the ^{13}C NMR spectrum in acetone-d_6 at room temperature does not show the signals corresponding to pyrazole carbons C-3 and C-5. Lowering the temperature to 223 K makes these signals appear with a $\Delta\delta$ = 10 ppm (the signals corresponding to C-2' carbon atoms bonded to the OH groups are also split and appear at 154.9 and 157.0 ppm). The ^{13}C CPMAS NMR spectrum confirms that in the absence of prototropy pyrazole **4** presents well resolved signals at 98.1 (C-4), 143.3 (C-5) and 152.5 and 153.2 ppm (C-3 and C-2').

X-ray Diffraction Studies. Two perspective views of the molecular structure of compounds **1**, **3** and **4** showing the conformation of the molecules and the atom numbering scheme are shown in Fig.1. The O atom of the methoxy and hydroxyl groups are on opposite sides of the pyridine and pyrazole planes and they are directed towards the nitrogen or nitrogens of the central rings, except in **1** where the opposite situation is found in order to avoid the N···O lone pair repulsion. It is noteworthy that the internal angle at N1 is enlarged and the adjacent ones are reduced (Table 1) when comparing compounds **1** and **3** as a consequence of the protonation. However, the N1-C2 and N1-C6 bonds are slightly longer than those of the neutral compound **1**. The phenyl rings, in **1**, are twisted with respect to the central one by 45° on average (Table 1). The presence of weak and strong intramolecular hydrogen bonds in **3** and **4** cause this angle to be reduced by ca 20° and 40°, respectively with the consequent increase of the conjugation with the pyridine or pyrazole, that is reflected in the length of the interannular C-C bonds. The methoxy groups in **1** are coplanar with the phenyl rings, giving rise to exocyclic angular distortions at the atom to which they are bonded (C8 and C16) as well as at C2 and C6. The ipso angles at C7 and C15 differ significantly from 120°. The rings in the molecule of **4** are almost planar (Table 1) which is indicative of an extension of the delocalized π-bonding system across the rings.

The pyridine molecule in **1**, presents no significant differences with the values reported for the two neutral analogous molecules retrieved from the Cambridge Structural Database[17] (October 1996 release) (CSD refcodes: VURYOW[18] and VURYEM[18]) and the same happens with molecule **3** with respect to the cation reported so far (WAMKIE[19]).

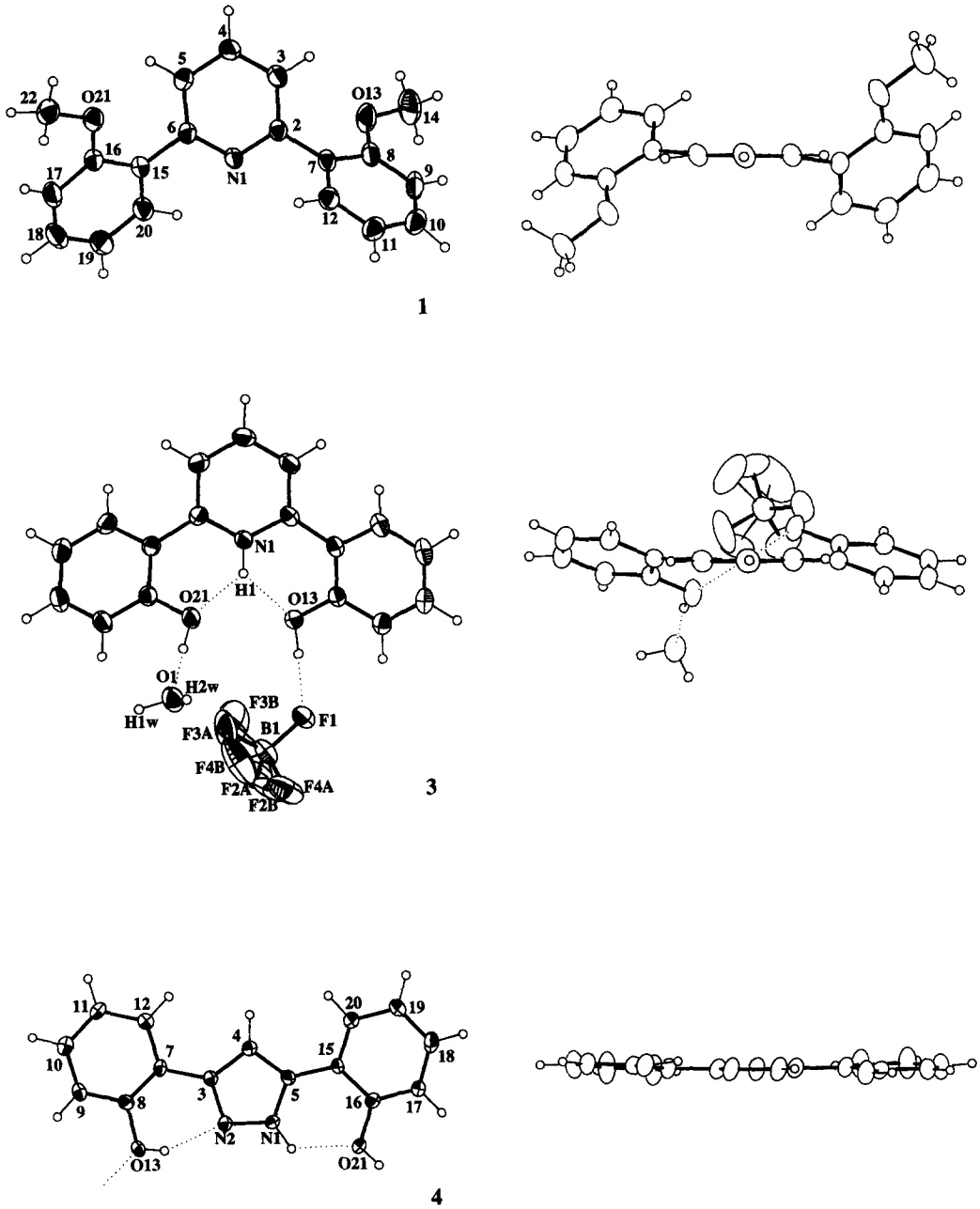


Fig.1.- Displacement ellipsoid plots of **1, 3** and **4** (30% probability level) showing the atom labelling and the conformation of the molecules.

Table 1. Selected geometrical parameters (Å,°).

Compound	1	3	Compound	1	3
N1-C2	1.343(3)	1.355(2)	C2-C7	1.486(4)	1.475(3)
N1-C6	1.352(3)	1.359(3)	C6-C15	1.489(4)	1.469(3)
C2-C3	1.386(5)	1.386(3)	C8-O13	1.369(5)	1.366(2)
C3-C4	1.383(4)	1.377(3)	C16-O21	1.360(3)	1.359(2)
C4-C5	1.378(4)	1.380(3)	O13-C14	1.420(7)	-
C5-C6	1.379(4)	1.386(3)	O21-C22	1.424(4)	-
C2-N1-C6	118.3(2)	125.4(2)	C5-C6-C15	123.4(3)	123.6(2)
N1-C2-C3	122.2(3)	117.2(2)	N1-O6-C15	114.3(2)	119.4(2)
C2-C3-C4	119.0(3)	119.7(2)	C8-C7-C12	118.6(3)	117.3(2)
C3-C4-C5	119.1(3)	121.0(2)	C7-C8-O13	115.6(3)	118.3(2)
C4-C5-C6	119.2(3)	119.8(2)	C9-C8-O13	124.6(3)	120.6(2)
C5-C6-N1	122.2(2)	117.0(2)	C16-C15-C20	118.1(2)	117.6(2)
N1-C2-C7	115.3(2)	119.4(2)	C15-C16-O21	116.0(2)	118.1(2)
C3-C2-C7	122.4(3)	123.4(2)	C17-C16-O21	124.3(3)	121.6(2)
N1-C2-C7-C8	130.4(3)	22.2(3)	C9-C8-O13-C14	-5.2(5)	-
N1-C6-C15-C16	136.2(3)	25.3(3)	C17-C16-O21-C22	2.5(5)	-

Compound	4				
N1-N2	1.359(3)	N1-C5	1.347(4)	N2-C3	1.335(4)
C3-C4	1.400(4)	C4-C5	1.376(4)	C3-C7	1.468(4)
C5-C15	1.470(4)	C8-O13	1.378(3)	C16-O21	1.364(63)
N2-N1-C5	112.4(2)	N1-N2-C3	105.2(2)	C2-C3-C4	110.3(2)
C3-C4-C5	106.3(3)	C4-C5-N1	106.0(2)	N2-C3-C7	119.9(2)
C4-C3-C7	129.8(3)	C4-C5-C15	131.2(3)	N1-C5-C15	122.8(2)
C8-C7-C12	117.4(3)	C7-C8-O13	121.1(2)	C9-C8-O13	117.3(3)
C16-C15-C20	117.4(3)	C15-C16-O21	117.5(2)	C17-C16-O21	121.4(2)
N2-C3-C7-C8	3.8(4)	N1-C5-C15-C16	4.5(4)		

Hydrogen interactions:

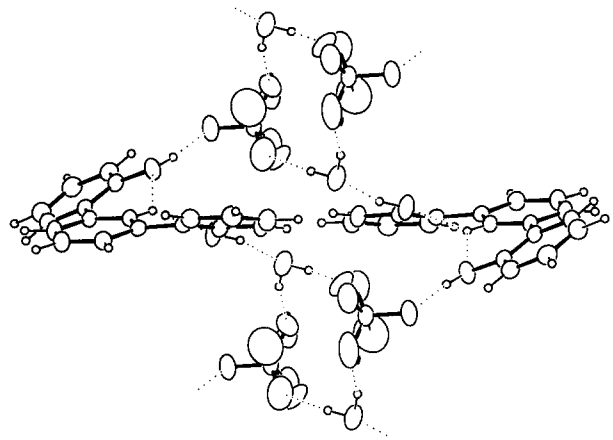
Compound **3:**	X-H	X...Y	H...Y	X-H...Y
N1-H1...O13	0.90(3)	2.631(2)	1.99(3)	127(2)
N1-H1...O21	0.90(3)	2.642(2)	2.01(3)	127(2)
O13-H13...F1	0.93(4)	2.657(2)	1.73(4)	172(3)
O21-H21...O1	0.94(4)	2.647(2)	1.73(3)	166(3)
O1-H1w...F3A(1-x,-y,-z)	0.95(5)	2.771(6)	1.83(5)	176(4)
O1-H1w...F4B(1-x,-y,-z)	0.95(5)	2.960(12)	2.09(5)	152(3)
O1-H2w...F3B(x,-1+y,z)	0.85(5)	2.722(14)	1.91(5)	158(4)
O1-H2w...F2A(x,-1+y,z)	0.85(5)	2.820(6)	2.02(4)	155(4)
Compound 4:				
N1-H1...O21	0.94(3)	2.595(3)	2.04(4)	116(3)
O13-H13...N2	0.95(4)	2.579(3)	1.71(4)	149(4)
O21-H21...O13(1/2-x, 1/2-y,- 1/2+z)	0.92(4)	2.693(3)	1.79(4)	165(4)

There are no unusual intermolecular distances in **1**. In the monohydrate salt, **3**, whilst the pyridinium proton forms intramolecular interactions with the hydroxyl groups, one OH takes part in a strong and rather unusual interaction with the F1 of the BF_4^- ion and the other with the water molecule (Fig. 1). It has been shown that organic fluorine (covalently bound to C atoms) hardly accepts hydrogen bonds;[20] however, short interactions with BF_4^- anions have also been detected with the N^+-H group acting as donor.[21] The ions are arranged in the crystal in centrosymmetric dimers that form chains along the **b** axis through the water molecules and the BF_4^- anions (Fig. 2a). In **4**, there are two intramolecular hydrogen bonds, between the hydroxyl H atom and the nearest N of the pyrazole and between the N-H and the other contiguous hydroxyl group (Fig. 1 and 2b). The hydroxyl groups are also involved in intermolecular hydrogen bonds responsible for the formation of chains (Fig. 2b) along the **a** axis.

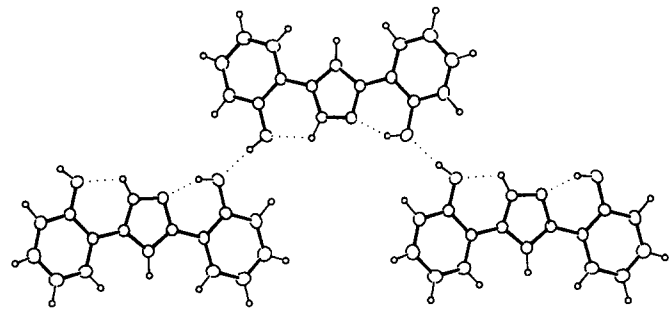
Although the structure of **2** could not be refined properly, the conformation of the three independent molecules can be established unambiguously. Futhermore, and using the results of the semiempirical calculations (see below) even the hydrogen bond network could be described. The molecules are not planar (each phenyl ring being rotated 24 and 31° on average over the three independent molecules) and they are grouped in chains (Fig. 2c), so that one hydroxyl group of molecule B is interacting with other of molecule C and so on along the **a** axis. An analogous chain is found with molecule A and their symmetry related ones through a glide plane (1/2+x, 1/2-y, z).

Semiempirical calculations. The conformation of molecules and the secondary structure of compounds **1**, **2**, **3** and **4** have been analyzed by means of AM1 semiempirical calculations.[22] The computed geometries show, in all cases, that the strength of the intramolecular hydrogen bonds is underestimated, as it is evidenced by the higher absolute values of the angles between planes in compounds **2**, **3** and **4**. In **1**, where no intramolecular hydrogen bond is possible, the calculated N1-C2-C7-C8 = N1-C6-C15-C16 torsion angles (135.7°) as well as the conformation of the methoxy groups (C-C-O-Me = 14.3°), Table 1 and Fig. 1 are close to the experimental ones .

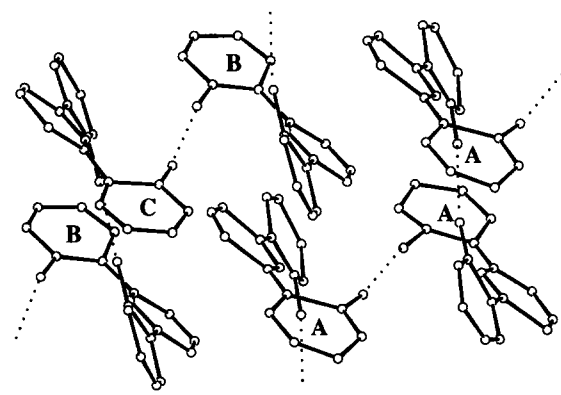
When intra and intermolecular hydrogen bonds occur, as in **2**, **3** and **4**, the smallest structural unit needed to reproduce the topological connectivity of the experimental network has been optimized, i.e., two molecules in **2**, one centrosymmetric dimer formed by two pairs of ions and two water molecules in **3** and one molecule in **4** (Fig. 2). In **2** and **4** the overall experimental hydrogen bond network has been obtained, the most significant differences being the lower coplanarity between the central and the substituent rings (torsion angles of 46.7 and 52.4° for **2** and -27.7 and -41.4° for **4**). The difference observed in **2**, both experimental and theoretically, could be related to the fact that the OH group attached to the phenyl ring, which presents the higher torsion angle, is acting as donor in the intermolecular O-H···O hydrogen bond that gives rise to chains of molecules, while the other is responsible for the formation of an O-H···N intramolecular bond and therefore, induces greater coplanarity of this aryl with respect to the central ring. In **3**, the AM1 parametrization is not able to reproduce the intermolecular hydrogen bond network. However, the optimized geometry shows the opening of the angle at the pyridinium protonated nitrogen (122.0°) and a lower degree of planarity (torsion angles of 36.9°) in spite of the N^+-H···OH intramolecular hydrogen bonds.



(a)



(b)



(c)

Fig.2.- (a) and (b). Views of part of the hydrogen bond network in the crystal structures of **3** and **4**. (c) illustrates the conformation of the three independent molecules (A, B and C) and the hydrogen bond system in **2.**

EXPERIMENTAL SECTION

Synthesis.- Melting points were determined on a Buchi 510 and Reichert-Thermovar instruments and are uncorrected. ^{1}H FT-NMR spectra were recorded in dilute solutions (*ca.* 0.3%) at 200 or 300 MHz on Varian Gemini 200 and Bruker AMX300 spectrometers. The chemical shifts were measured relative to TMS. ^{1}H Assignments were made using an COSY (^{1}H/^{1}H) experiment while ^{13}C assignments were made using an HETCOR (^{1}H/^{13}C) experiment as well as one-dimensional selective INEPT (longe-range C/H couplings were optimized to 7 Hz). High resolution mass spectra were recorded using a VG Autospec spectrometer. 13C NMR CPMAS spectrum was recorded at 100 MHz on a Bruker MSL400 spectrometer with the following conditions: 5 s of recycle delay, 90° pulse of 5.45 μs and sw = 35211.3 Hz (350 ppm), AQ = 0.116 s. Mass spectra were determined on a VG2-250 quadrupole mass spectrometer (electron impact). Elemental analyses were carried out with a Fisons EA-1108 apparatus.

Experimental procedure used for pyridine derivatives

1-*N*,*N*-dimethylamino-3-(2'-methoxyphenyl)-3-oxo-1-propene **11**. A mixture of 2'-methoxyacetophenone **10** (4 mL, 29 mmol) and *N*,*N*-dimethylformamide dimethylacetal (7.7 mL, 58 mmol) was heated at 110 °C for 18 h. Concentration under reduced pressure of the reaction mixture left an orange oil. The residue was dissolved in dichloromethane and the resulting solution was washed with water and then with brine. After drying over sodium sulfate, evaporation of the solvent afforded the crude product. Purification was performed by flash chromatography over silica gel using ethyl acetate then methanol as eluent giving 3.77 g (63%) of an orange viscous oil. ^{1}H NMR ($CDCl_3$) δ 7.60-7.20 (m, 3H), 6.95 (m , 2H), 5.53 (d, 1H), 3.84 (s, 3H), 3.03 (s, 3H), 2.87 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 156.6, 154.2, 147.7, 131.3, 130.3, 129.0, 120.1, 111.2, 97.8, 55.5, 44.6, 37.0. IR (cm^{-1}, neat) : 1640 (ν_{CO}). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.33; H, 7.01; N, 6.91.

2,6-Bis-(2'-methoxyphenyl)pyridine **1**. To a solution of potassium *t*-butoxide (1.10 g, 10 mmol) in dry tetrahydrofuran previously decanted was added the 2'-methoxyacetophenone **10** (0.73 g , 4.8 mmol). A yellow solid in suspension appeared. After stirring 2 h at room temperature 1-*N*,*N*-dimethylamino-3-(2'-methoxyphenyl)-3-oxo-1-propene **11** in a small amount of dry tetrahydrofuran was added in one portion. The reaction mixture was stirred at room temperature overnight and became a dark-red solution. A solution of ammonium acetate (3.85 g) in 25 mL glacial acetic acid was added. Most of the tetrahydrofuran was slowly distilled off during 2 h. Finally, all organic solvents were removed under reduced pressure. The orange oil obtained was dissolved in dichloromethane and washed with a saturated solution of sodium bicarbonate until the pH remained basic. The combined aqueous layers were extracted several times with dichloromethane and the combined organic extracts were washed with water and brine. After drying over sodium sulfate and evaporation under reduced pressure a dark orange oil was obtained. Purification by flash chromatography over silica gel using hexane, ethyl acetate 90:10 as eluent gave 0.86 g (60%) of a beige solid, mp 117 °C. Transparent prisms suitable for X-ray diffraction obtained from ethyl acetate. MS (EI$^+$) 291 ($M^{+\cdot}$, 95%), 290 (100%), 275 (9%), 260 (28%). ^{1}H NMR ($CDCl_3$) δ 7.92 (dd, 2H), 7.76 (m, 2H), 7.36 (m, 2H), 7.10-7.00 (m, 4H), 3.88 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 157.6, 155.9, 135.7, 132.0, 130.2, 130.1, 123.6, 121.6, 111.9, 56.1. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.41; H, 6.07; N, 4.79.

2,6-Bis-(2'-hydroxyphenyl)pyridine **2**. In a round-bottom flask equipped with a reflux condenser, were mixed 2,6-bis-(2'-methoxyphenyl)pyridine **1** (finely ground, 1.30 g, 4.5 mmol) and pyridinium hydrochloride

(14 g, 1.35 mol) . The mixture was heated under nitrogen flow to 210 °C (near reflux temperature) for 1 h. After cooling, water (100 mL) was added and the aqueous solution was extracted with dichloromethane (5 x 30 mL). Combined organic extracts were washed with water, dried over sodium sulfate and concentrated to yield a beige solid. Chromatography over alumina using hexane, ethyl acetate 75:25 as eluent afforded a pale yellow solid. The resulting hydrochloride salt was dissolved in dichloromethane and washed with a sodium bicarbonate saturated solution. The organic layer was dried over sodium sulfate then evaporated to give 0.73g (63%) of a pale yellow solid, mp 138 °C. Small needles for X-ray diffraction were obtained by water diffusion in an ethanol solution. ^{1}H NMR ($CDCl_3$) δ 10.00 (br, 2H), 7.96 (t, 1H), 7.69 (d, J = 8 Hz, 2H), 7.60 (dd, J = 8 and 3 Hz, 2H), 7.34 (td, J = 10, 2 and 2 Hz, 2H), 6.90 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 156.6, 156.1, 139.5, 131.5, 128.1, 121.6, 120.0, 119.8, 118.0. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.61; H, 5.10; N, 5.19.

Bis-2,6-(2'-hydroxyphenyl)pyridinium **3** tetrafluoroborate. Crystals of compound **3**.BF_4^-.H_2O were obtained adding 35% tetrafluoroboric acid (0.4 mL, 0.38 mmol) to a solution of bis-2,6-(2'-hydroxyphenyl) pyridine **2** (100 mg, 0.38 mmol) in dichloromethane (20 mL), mp 235 °C. Parallelepipedic crystals suitable for X-ray diffraction were obtained from dichloromethane.

Experimental procedure used for pyrazole derivatives

2'-Benzyloxybenzoic acid **13**. A mixture of salicylic acid (20 g, 145 mmol), potassium carbonate (120.2 g, 870 mmol) and benzyl chloride (28.6 mL, 348 mmol) in *N,N*-dimethylformamide (160 mL) was refluxed, under nitrogen, for 2 h. After cooling, the organic salts were filtered off and the resulting solution was poured into a mixture of ice and water. This mixture was extracted with chloroform (4 x 150 mL) and the organic layer passed through anhydrous sodium sulfate. After evaporation of the solvent, the intermediate ester (36.5 g, 79,2 %) was used without further purification.

A solution of the ester (32 g, 100.6 mmol) in methanol (200 mL) was added to an aqueous solution of sodium hydroxide (17g/40mL), and the resulting mixture was heated at 60-70 °C, under nitrogen, during ca. 3 h. After cooling, the reaction mixture was poured into ice and water and the pH adjusted to p$H \approx 4$ with diluted hydrochloric acid. The solid which was formed was removed by filtration, dissolved in chloroform (200 mL) and washed with water. The organic layer was passed through anhydrous sodium sulfate and the solvent evaporated to dryness. The 2'-benzyloxybenzoic acid **13** (14.4 g, 55 %) was crystallized from hot ethanol: mp 67-70 °C. ^{1}H NMR 5.30 ($\underline{CH_2}$, s), 7.14 (H-3, dd, J = 8.8 and 1.3 Hz), 7.16 (H-5, ddd, J = 8.0, 7.2 and 1.3 Hz), 7.36-7.46 (H-2',3',4',5',6', m), 7.56 (H-4, ddd, J = 8.8, 7.2 and 1.9 Hz), 8.21 (H-6, dd, J = 8.0 and 1.9 Hz); ^{13}C NMR 72,3 ($\underline{C}H_2$), 113.0 (C-3), 118.0 (C-1), 122.5 (C-5), 128.0 (C-2',6'), 129.2 (C-4'), 129.2 (C-3',5'), 133.9 (C-6), 134.2 (C-1'), 135.0 (C-4), 157.3 (C-2), 165.3 (C=O); EIMS m/z (rel int) 228 ($M^{+\cdot}$, 15), 183 (4), 105 (4), 92 (22), 91 (100),77 (4), 65 (25). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30; Found: C, 74.52; H, 5.44.

2'-(2''-Benzyloxybenzoyloxy)acetophenone **14**. 2'-Benzyloxybenzoic acid **13** (8.2 g, 36 mmol) and phosphoryl chloride (7,4 mL, 79.4 mmol) were added to a solution of 2'-hydroxyacetophenone **12** (2.6 mL, 30 mmol) in dry pyridine (20 mL). The resulting mixture was heated at 100 °C, under nitrogen, during 24 h. After cooling, the reaction mixture was poured into ice and water and the pH adjusted to pH ≈ 5 with diluted hydrochloric acid. The solid which was formed was removed by filtration, dissolved in dichlomethane (20 mL) and purified by silica gel column chromatography, using dichloromethane as eluent. After evaporation of the solvent to dryness the 2'-(2''-benzyloxybenzoyloxy)acetophenone **14** (6.48 g , 52.0 %) was crystallized from

hot ethanol: mp 77-78 °C. ^{1}H NMR δ 2.38 (C$\underline{H}_3$, s), 5.03 (C$\underline{H}_2$, s), 6.91 (H-5", dd, *J* = 7.6 and 7.1 Hz), 6.92 (H-3", d, *J* = 5 Hz), 7.04 (H-3', dd, *J* = 8.1 and 1.1 Hz), 7.08-7.21 (H-3"', 4"', 5', 5"', m), 7.31-7.40 (H-2"', 4', 4",6"', m), 7.68 (H-6', dd, *J* = 7.8 and 1.7 Hz), 7.98 (H-6", dd, *J* = 7.6 and 1.8 Hz); ^{13}C NMR δ 29.5 (C-2), 72.3 (C$\underline{H}_2$), 113.6 (C-3"), 119.1 (C-1"), 120.5 (C-5"), 123.8 (C-3'), 125.8 (C-5'), 126.8 (C-2"',6"'), 127.6 (C-4"'), 128.3 (C-3"',5"'), 130.0 (C-6'), 131.2 (C-1'), 131.3 (C-6"), 133.2 (C-4"), 134.3 (C-4'), 136.3 (C-1"'), 149.2 (C-2'), 158.6 (C-2"), 164.0 (C=O), 197.5 (C-1); EIMS m/z (rel int) 346 ($M^{+\cdot}$, 0.2), 345 (0.2), 212 (23), 211 (80), 136 (12), 120 (14), 92 (36), 91 (100), 83 (9), 77 (7), 65 (20). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24; N. Found: C, 75.98; H, 5.09.

2-Benzyloxy-2',β-dihydroxychalcone **15.** Sodium hydride (334 mg, 13.9 mmol) was added to a solution of 2'-(2"-benzyloxybenzoyloxy)acetophenone **2** (4.8 g, 13.9 mmol) in dry tetrahydrofuran (200 mL). The mixture was refluxed, under nitrogen, during 2 h. After cooling, the reaction mixture was poured into ice and water and the pH adjusted to ca. 6 with diluted hydrochloric acid. The solid which was formed was removed by filtration, dissolved in dichloromethane (20 mL) and purified by silica gel column chromatography, using dichloromethane as eluent. After evaporation of the solvent to dryness the 2-benzyloxy-2',β-dihydroxychalcone **15** (2.7 g, 56.1 %) was crystallized from hot ethanol, mp 144-147 °C. ^{1}H NMR δ 5.15 (C$\underline{H}_2$, s), 6.55 (H-5', ddd, *J* = 8.2, 7.6 and 1.6 Hz), 6.90 (H-3', dd, *J* = 7.9 and 1.6 Hz), 6.91 (H-6', dd, *J* = 8.2 and 1.1 Hz), 7.12 (H-5, dd, *J* = 7.9 and 7.3 Hz), 7.13 (H-3, d, *J* = 7.3 Hz), 7.35 (H-4', ddd, *J* = 7.9, 7.6 and 1.1 Hz), 7.36 (H-α, s), 7.43-7.56 (H-2",3",4,4",5",6", m), 8.12 (H-6, dd, *J* = 7.9 and 1.7 Hz), 12.19 (O$\underline{H}$-2', s), 15.61 (O$\underline{H}$-b, s); ^{13}C NMR δ 71.1 (C$\underline{H}_2$), 97.7 (C-a), 112.4 (C-3), 118.3 (C-3'), 118.9 (C-5'), 119.2 (C-1'), 121.1 (C-5), 122.0 (C-1), 128.7 (C-2".4", 6',6"), 128.9 (C-3",5"), 130.2 (C-6), 133.3 (C-4), 135.3 (C-4'), 135.7 (C-1"), 158.2 (C-2), 162.3 (C-2'), 174.1 (C-b), 196.1 (C=O); EIMS m/z (rel. int.) 346 ($M^{+\cdot}$, 22), 328 (5), 311 (8), 238 (25), 225 (17), 211 (15), 210 (28), 121 (49), 91 (87), 87 (25), 85 (74), 83 (100). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24; N. Found: C, 76.13; H, 5.21.

3(5)-(2'-Hydroxyphenyl)-5(3)-(2"-benzyloxyphenyl)pyrazole **16**. Hydrazine monohydrate (0.84 mL, 17.3 mmol) was added to a solution of the 2-benzyloxy-2',β-dihydroxychalcone **15** (2.4 g 6.9 mmol) in methanol (1 L). The mixture was stirred, under nitrogen, during 12 h, then the solvent was evaporated to dryness. Water (200 mL) was added to the residue and the mixture was acidified to pH 6 with diluted acetic acid and extracted with chloroform (3 x 150 mL). After evaporation of the solvent to dryness the 3(5)-(2'-hydroxyphenyl)-5(3)-(2"-benzyloxyphenyl)pyrazol **16** (1.9 g, 80.5 %) was crystallized from hot ethanol: mp 90-92 °C. ^{1}H NMR δ 5.22 (C$\underline{H}_2$, s), 6.97 (H-5', ddd, *J* = 7.6, 7.4 and 1.2 Hz), 7.01 (H-4, s), 7.08 (H-3', dd, *J* = 8.1 and 1.2 Hz), 7.10 (H-3", d, J 7.8 Hz), 7.12 (H-5", ddd, *J* = 7.9, 7.8 and 1.0 Hz), 7.26 (H-4', ddd, *J* = 8.1, 7.4 and 1.6 Hz), 7.41-7.45 (H-2"', 3"', 4"', 5"', 6"', aromatic protons of the Bn substituent, m), 7.34 (H-4", dt, *J* = 7.8 and 1.7 Hz), 7.66 (H-6', dd, *J* = 7.6 and 1.6 Hz), 7.79 (H-6", dd, *J* = 7.9 and 1.7 Hz), 11.00 (O$\underline{H}$-2', s broad), 11.49 (N$\underline{H}$, s very broad); ^{13}C NMR δ 71.0 (C$\underline{H}$2), 98.9 (C-4), 112.9 (C-3"), 116.6 (C-1"), 116.9 (C-1'), 117.0 (C-3'), 119.1 (C-5'), 121.8 (C-5"), 126.4 (C-6'), 127.7 (C-2"', 6"'), 128.2 (C-6"), 128.7 (C-4"'), 129.1 (C-4'), 129.1 (C-3"', 5"'), 129.8 (C-4"), 135.6 (C-1"'), 141.3 (C-5), 151.5 (C-3), 155.0 (C-2"), 156.0 (C-2'); EIMS m/z (rel. int.) 342 ($M^{+\cdot}$, 95), 341 (32), 325 (9), 265 (15), 252 (20), 251 (15), 223 (10), 222 (11), 165 (20), 132 (11), 91 (100). Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.36; H, 5.41; N, 7.91.

3,5-Bis(2'-hydroxyphenyl)pyrazole **4**. Ammonium formate (1.7 g, 27 mmol) and 10 % palladium on charcoal (92 mg) were added to a solution of 3(5)-(2'-hydroxyphenyl)-5(3)-(2"-benzyloxyphenyl)pyrazol **4** (924 mg, 2.7 mmol) in acetone (150 mL). The mixture was refluxed, under nitrogen, during 1 h. After this period, the reaction mixture was filtered through celite, followed by evaporation of the solvent to dryness. The 3,5-bis(2'-hydroxyphenyl)pyrazol **4** (599 mg, 88.0 %) was crystalized from chloroform: mp 188-190 °C. ^{1}H NMR (acetone-d_6) δ 6.96 (H-5', dd, *J* = 7.8 and 7.5 Hz), 7.02 (H-3', d, *J* = 7.9 Hz), 7.23 (H-4', ddd, *J* = 7.9, 7.5 and 1.4 Hz), 7.33 (H-4, s), 7.82 (H-6', dd, *J* = 7.8 and 1.4 Hz) ca. 10 (very broad, NH and OH); ^{13}C NMR (acetone-d_6) δ 100.1 (C-4), 117.2 (C-1'), 117.3 (C-3'), 120.5 (C-5'), 128.1 (C-6'), 130.1 (C-4'), 155.9 (C-2'); at 293 K the signals of pyrazole carbons C-3 and C-5 are not observed; EIMS m/z (rel. int.) 252 ($M^{+\bullet}$, 100), 224 (13), 223 (19), 205 (9), 165 (11), 131 (13), 126 (10), 104 (8), 103 (10). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.35; H, 5.00; N, 10.89. Crystals suitable for X-ray diffraction were obtained from methanol.

X-ray Analysis.- A summary of data collection and refinement process is given in Table 2. The structures were solved by direct methods (SIR92)[23] and refined by least-squares procedures on Fobs. All hydrogens were obtained from difference Fourier synthesis and included and refined isotropically in the last cycles. The BF_4^- anion is disordered and has been split into two sites (A and B with population factors of 0.64(1) and 0.36(1) respectively) sharing the B1-F1 bond. Crystals of **2** were very thin (0.03 x 0.40 x 0.50 mm) and they broke during data collection. Two sets of data were recorded on a Philips PW1100 difractometer, however the crystals did not diffract strongly [only 58% of the data could be labelled as observed with $I>2\sigma(I)$; Crystal data: orthorhombic, **a** = 7.2046(4), **b** = 22.6425(44) **c** = 24.2534(34) Å, $Pna2_1$, Z = 12]. The three independent molecules were located fairly straightforwardly although the anisotropic refinement procedure did not improve and gave either unreliable displacement parameters or molecular geometry (R = 0.23 after the isotropic refinement). The location of the molecules in the unit cell eliminated the Pnam space group. Further attempts to obtain a better data set using a CCD Siemens Smart diffractometer were unsuccessful, therefore, the refinement procedure was stopped at this point. The scattering factors were taken from the International Tables for X-Ray Crystallography.[24] The calculations were carried out with the XTAL,[25] PESOS[26] and PARST[27] set of programs running on a DEC3000-300X workstation.[28]

Acknowledgements

We thank the Ministerio de Educación y Ciencia of Spain for financial support (DGICYT, Projects PB93-0197-C02-02 and PB93-0125). Thanks are given to the EU for the TMR network 'Localization and Transfer of Hydrogen' (No. CHRX CT 940582). Thanks are given to the University of Aveiro and JNICT for funding the Research Unit No. 62/94 and also to JNICT/PRAXIS XXI for a Grant (L.M.P.M.A. BTL/6303/95). Authors thank Dr. E. Gutierrez-Puebla for his helpful assistance in the diffractometry measurement on a CCD Siemens Smart equipment.

Table 2. Crystal analysis parameters at room temperature.

	1	3	4
Crystal data			
Formula	$C_{19}H_{17}NO_2$	$C_{17}H_{14}NO_2^+ \cdot BH_4^- \cdot H_2O$	$C_{15}H_{14}N_2O_2$
Crystal habit	Colourless, prism	Colourless, prism	Colourless, prism
Crystal size (mm)	0.17 x 0.33 x 0.50	0.17 x 0.30 x 0.50	0.30 x 0.30 x 0.50
Symmetry	Monoclinic, Ia	Monoclinic, $P2_1/n$	Tetragonal, I-42d
Unit cell determination:	Least-squares fit from 56 reflexions (θ<45°)	Least-squares fit from 78 reflexions (θ<45°)	Least-squares fit from 71 reflexions (θ<45°)
Unit cell dimensions (Å,°)	a=9.6185(5)	a=18.2809(12)	a=18.0893(5)
	b=22.7508(15)	b=7.2889(3)	b=18.0893(5)
	c=7.1502(3)	c=12.6497(8)	c=15.3714(6)
	β=99.936(5)	β=91.524(6)	–
Packing: V(Å³), Z	1541.2(2), 4	1685.0(2), 4	5029.9(3), 16
Dc(g/cm³), M, F(000)	1.256, 291.3, 616	1.455, 369.1, 760	1.343, 254.3, 2144
μ(cm^{-1})	6.49	11.06	7.35
Experimental data			
Technique	Four circle diffractometer: Philips PW1100, Bisecting geometry. Graphite oriented monochromator. $\omega/2\theta$ scans. Detector apertures 1 x 1°. 1 min./reflex. CuKα. θ_{max}= 65°. Scan width= 1.5°		
Number of reflexions:			
Independent	1214	2871	1193
Observed (2σ(I) criterion)	1172	2419	1069
Standard reflexions:	2 reflexions every 90 minutes. No variation		
Solution and refinement			
Solution		Direct methods: Sir92	
Refinement:			
Least-Squares on Fo		Full matrix	
Secondary extinction (10^4)	0.38(2)	0.66(3)	0.46(1)
Parameters:			
Number of variables	265	327	220
Degrees of freedom	907	2092	973
Ratio of freedom	4.4	7.4	4.9
Final shift/error	0.006	0.092	0.002
H atoms		From difference synthesis	
Weighting-scheme	Empirical as to give no trends in <wΔ^2F> vs. <|Fobs|> and<sinθ/λ>		
Max. thermal value (Å²)	U22[C14]=0.102(3)	U11[F2B]=0.21(2)	U22[C11]=0.128(3)
Final ΔF peaks (e$Å^{-3}$)	0.12	0.35	0.13
Final R and Rw	0.032, 0.035	0.046, 0.052	0.034,0.047

References

1. Elguero, J. Pyrazoles, in *Comprehensive Heterocyclic Chemistry, A Review of the Literature 1982-1995*, Pergamon, Oxford, **1996**, Vol. *3*, p. 29.
2. Watson, A. A.; House, D. A.; Steel, P. J. *Aust. J. Chem.*, **1995**, *48*, 1549. Steel, P. J. *Adv. Heterocycl. Chem.*, **1997**, *67*, 1.
3. Teixidor, F.; Escriche, L.; Rodríguez, I.; Casabó, J.; Rius, J.; Molins, E.; Martínez, B.; Miravitlles. C. *J. Chem. Soc., Dalton Trans.*, **1989**, 1381.
4. Parker, D.; Lehn, J.-M.; Rimmer, J. *J. Chem. Soc., Datlon Trans.*, **1985**, 1517.
5. Bouwman, E.; Driessen, W. L. *Acta Crystallogr., Sect. C*, **1989**, *45*, 1792; Bouwman, E.; Driessen, W. L.; Reedijk, Smykalla, C.; Smits, J. M. M.; Beurkens, P. T.; Laschi, F.; Zanello, P. *Inorg. Chem.*, **1990**, *29*, 4881. van Steenberger, A. C.; Bouwman, E.; de Graaff, R. A. G.; Driessen, W. L.; Reedijk, J.; Zanello, P. *J. Chem. Soc., Datlon Trans.*, **1990**, 3175.
6. Rodríguez-Ubis, J. C.; Sedano, R.; Barroso, G.; Juanes, O.; Brunet, E. Helv. Chim. Acta, **1997**, *80*, 86.
7. Shieh, S.-J.; Chou, C.-C.; Lee, G.-H.; Wang, C.-C.; Peng, S.-M. *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 56.
8. Jeffery, J. C.; Schatz, E.; Ward, M. D. *J. Chem. Soc., Dalton Trans.*, **1992**, 1921; Jeffery, J. C.; Ward, M. D. *J. Chem. Soc., Dalton Trans.*, **1992**, 2119; Holligan, B. M.; Jeffery, J. C.; Ward, M. D. *J. Chem. Soc., Dalton Trans.*, **1992**, 3337; Holligan, B. M.; Jeffery, J. C.; Norgett, M. K.; Schatz, E.; Ward, M. D. *J. Chem. Soc., Dalton Trans.*, **1992**, 3345. Jeffery, J. C.; Maher, J. P.; Otter, C. A.; Thornton, P.; Ward, M. D. *J. Chem. Soc., Dalton Trans.*, **1995**, 819. Bardwell, D. A.; Jeffery, J. C.; Ward, M. D. *J. Chem. Soc., Dalton Trans.*, **1995**, 3071.
9. Dijkstra, P. J.; den Hertog, H. J.; van Steen, B. J.; Zijlstra, S.; Skowronska-Ptasinska, M.; Reinhoudt, D. N.; van Eerden, J.; Harkema, S. *J. Org. Chem.*, **1987**, *52*, 2433; Grootenhuis, P. D. J.; van Eerden, J.; Dijkstra, P. J.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.*, **1987**, *109*, 8044; Dijkstra, P. J.; den Hertog, H. J.; van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.*, **1988**, *53*, 374.
10. Llamas-Saiz, A. L.; Foces-Foces, C.; Elguero, J.; Meutermans, W. *Acta Crystallogr., Sect. C*, **1992**, *48*, 714.
11. Ahmad, R.; Ahmad, N.; Zia-ul-Haq, M.; Wahid, A. *J. Chem. Soc. Pak.*, **1996**, *18*, 38.
12. Sacquet, M.-C.; Fargeau-Bellassoued, M.-C.; Graffe, B. *J. Heterocycl. Chem.*, **1991**, *28*, 667; Singh, S. P.; Kumar, D. *Synth. Commun.*, **1996**, *26*, 3193.
13. Halcrow, M. A.; Powell, H. R.; Duer, M. J. *Acta Crystallogr., Sect. B*, **1996**, *52*, 746.
14. Erdtman, H.; Granath, M.; Schultz, G. *Acta Chem. Scand.* **1954**, *8*, 1442.
15. Elguero, J. 'Pyrazoles and their Benzo Derivatives', in *Comprehensive Heterocyclic Chemistry*, Vol. 5, p. 167, Katritzky, A. R.; Rees, C. W. Eds., Pergamon Press, Oxford, **1984**.
16. Begtrup, M.; Boyer, G.; Cabildo, P.; Cativiela, C.; Claramunt, R. M.; Elguero, J.; García, J. I.; Toiron, C.; Vedsø, P. *Magn. Reson. Chem.*, **1993**, *31*, 107.
17. Allen, .H.; Davies, J.E.; Galloy, J.J.; Johnson, O.; Kennard, O.; Macrae, C.F.; Mitchell, E.M.; Mitchell, J.F.; Smith, J.M.; Watson, D.G. *J. Chem. Info. Comput. Sci.* **1991**, *31*, 187.
18. Bessel, C. A.; See, R. F.; Jameson, D. L.; Churchill, M. R.; Takeuchi, K. J. *J. Chem. Soc., Dalton Trans.*, **1992**, 3223.
19. Kumbhar, A. S.; Padhye, S. B.; Puranik, V. G.; Dhaneshwar, N. N.; Tavale, S. S.; Kelkar, A. A.; Chaudhari, R. V. *J. Mol. Catal.*, **1992**, *75*, 187.
20. Dunitz, J. D.; Robin. R. *Chem. Eur.J.*, **1997**, *3*, 89.
21. Llamas-Saiz, A. L.; Foces-Foces, C.; Elguero, J.; Molina, P.; Alajarin, M. Vidal, A. *J. Chem. Soc. Perkin Trans 2*, **1991**, 1667.
22. Stewart, J. J. P. *J. Comput.-Aided Mol. Des.*, **1990**, *4*, 1.
23. Altomare, A.; Burla, M.C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. SIR92, *J. Appl. Cryst.* **1994**, *27*, 435.
24. *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham, England, 1974.
25. Hall, S.R.; Flack, H.D.; Stewart, J.M. 'Xtal3.2', Ed. Univ. of Western Autralia, Perth, 1994.
26. Martínez-Ripoll, M.; Cano, F.H. 'PESOS', unpublished program.
27. Nardelli, M. *Comput. Chem.* **1983**, *7*, 95.
28. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 2EZ, UK.

(*Received in UK* 24 *March* 1997; *revised* 25 *June* 1997; *accepted* 26 *June* 1997)