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The synthesis of pyridazine functionalized with dioximes side chains are described. Several 3,6-disubstituted pyridazine derivatives were prepared and their structures determined by spectroscopic methods (nmr, ir and ms).

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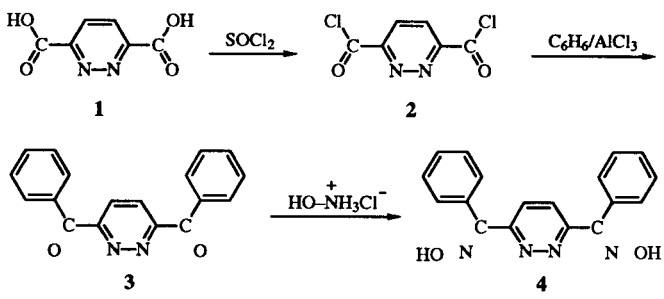
Introduction.

Polymetallic complexes are ubiquitous in nature as active sites in a variety of metalloenzymes [1-3] and are playing a significant and expanding role as industrial chemical catalysis [4]. The importance of multimetallic species has promoted a wide range of theoretical treatments concerning their properties. These include orbital models for magnetic exchange coupling [5,6] and for electrical conductivity [7]. Dinucleating ligands are attractive systems to control in a systematic manner the disposition and the separation of metal ions in homo and hetero binuclear complexes. In an effort to obtain novel binuclear planar macrocyclic complexes [8] with an organic backbone stable against chemical and electrochemical oxidation, we have synthesized pyridazine functionalized with dioxime side chains. The precursors of such compounds must contain electron withdrawing functions like carbonyl and carboxylic groups. Unfortunately, very little is known about the synthesis of these products in preparative quantities. In the course of our synthetic studies on pyridazine derivatives, we have reported the synthesis and X-ray structure of 3,6-dicarboxypyridazine (**1**) [9] and 3,6-dihydroxymethylpyridazine (**7**) [10]. These compounds provide routes to new variously 3,6-disubstituded pyridazines. This paper describes these results.

Results.

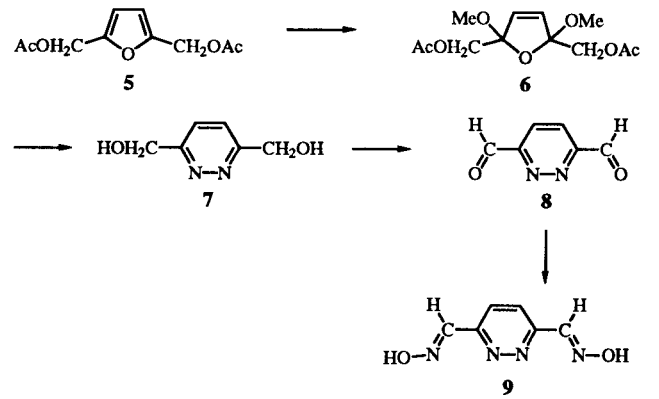
The diacid **1** was converted into 3,6-pyridazinedicarbonyl chloride (**2**) in quantitative yield using excess thionyl chloride, containing a few drops of dimethylformamide. The product fumed in a humid atmosphere but it could be handled in dry air. To avoid hydration, compound **2** was immediately suspended in anhydrous benzene. Anhydrous aluminium chloride was slowly added to the mixture with vigourous stirring to avoid the formation of a non-stirrable cake during the reaction. After heating at 60-65° during 4 hours, solution was complete and evolution of hydrogen chloride had ceased. The mixture was hydrolysed to give 3,6-dibenzoylpyridazine (**3**) in 60% yield. Treatment of **3** with a mixture of hydroxylamine hydrochloride and sodium hydroxide gave the 3,6-dibenzoylpyridazine dioxime **4** in nearly quantitative yield (Scheme 1).

Scheme 1



A different procedure was used for the synthesis of 3,6-diformylpyridazine dioxime (**9**, Scheme 2). The first step involves the preparation of 3,6-dihydroxymethylpyridazine (**7**). Compound **7** was previously prepared using 2,5-dihydroxymethylfuran as the starting product [11]. We have modified this procedure in order to obtain the diol **7** without isolating the intermediate 2,5-dimethoxy-2,5-dihydrofuran **6**. Compound **7** was then oxidized to 3,6-

Scheme 2



diformylpyridazine (**8**) with dimethyl sulfoxide activated by oxalyl chloride at low temperature using a methylene chloride/dimethyl sulfoxide mixed solvent [12]. The dialdehyde **8** was not isolated; the dioxime **9** precipitated directly from the aqueous layer after addition of an excess of hydroxylamine hydrochloride (Scheme 2).

EXPERIMENTAL

Melting points (uncorrected) were determined using a Kofler block bench apparatus. The ^{1}H-nmr spectra were recorded on a Hitachi Perkin Elmer 60 MHz spectrometer using tetramethylsilane as internal standard. The ^{13}C-nmr spectra were recorded on a Bruker WP 80 MHZ using dichloromethane and methanol as the internal reference. Mass spectra were taken on a Ribermag R10-10 apparatus using a direct inlet system. Infrared spectra were obtained on a Perkin Elmer spectrophotometer 1310 as potassium bromide pellets. Microanalyses for C, H, N and O were performed by the Service Central d'Analyses du CNRS, Versaison, France.

3,6-Pyridazinedicarbonyl Chloride (**2**).

To a solution of **1** (8.4 g, 0.05 mole) in thionyl chloride (30 ml), dimethylformamide (1 ml) was added. The mixture was heated under reflux for 3 hours, until evolution of hydrogen chloride had ceased. Unreacted thionyl chloride was removed under reduced pressure at nearly room temperature. The residue was treated with anhydrous pentane to yield **2** as a crystalline yellow solid (8.9 g, 98%) and then used in the next step without further purification; ^{1}H-nmr (chloroform-d): δ 8.4 (s, 1H heterocycle); ^{13}C-nmr (chloroform-d): δ 154 (s, C=N), 128 (s, C=C), 163 (s, C=O).

3,6-Dibenzoylpyridazine (**3**).

To a suspension of **2** (7.3 g, 0.04 mole) in anhydrous benzene (50 ml), anhydrous aluminium chloride (16 g, 0.12 mole) was added in small portions over a period of 30 minutes. The mixture was warmed at 60-65° with vigorous stirring for 4-5 hours, until evolution of hydrogen chloride ceased. After cooling, the mixture was then poured into water and made only slightly acidic (*p*H 5-6) with sodium carbonate solution and extracted with ether. The extract was washed with water, dried (magnesium sulfate) and concentrated to dryness. The dark brown residue was vigorously stirred under reflux with petroleum ether (100 ml). After decantation, the petroleum ether solution was rapidly cooled at about -80° using liquid nitrogen to yield a white crystalline solid. This process was repeated 3 or 4 times until no crystalline product appeared on cooling. Recrystallization from petroleum ether gave **3** (7 g, 60%); ^{1}H-nmr (chloroform-d): δ 7.4-7.7 (m, 3H, 3,4, 5-positions of benzoyl), 8.3-8.5 (m, 2H, 2,6-positions of benzoyl), 8.35 (s, 1H, pyridazine); ir: cm^{-1} 1660 (C=0); ms: m/z 288 (9, M$^+$), 155 (14), 105 (100), 77 (72), 51 (11).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72; O, 11.10. Found: C, 75.18; H, 4.25; N, 9.63; O, 10.98.

3,6-Dibenzoylpyridazine Dioxime (**4**).

A mixture of **3** (5.8 g, 0.02 mole), sodium hydroxide (2.4 g, 0.06 mole), hydroxylamine hydrochloride (3.5 g 0.05 mole), methanol (5 ml) and water (5 ml) was stirred at room temperature for 3 hours. A pasty product was obtained and treated with water [11]. A little insoluble solid was filtered off. The filtrate was neutralized with hydrochloric acid and the insoluble crystalline solid was recrystallized from ethanol to yield **4** (6 g, 95%). Recrystallisation from chloroform gave a pure sample, mp 228°; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.3-8.0 (m, 10H, Ph-H), 8.35 (s, 2H, pyridazine), 11 (br, 2H, exch OH); ms: m/z 318 (8, M$^+$), 287 (3), 168 (11), 149 (11), 118 (29), 115 (33), 103 (29), 83 (100), 77 (52), 70 (20).

Anal. Calcd. for $C_{18}H_{14}N_4O_2$: C, 67.92; H, 4.43; N, 17.60; O, 10.05. Found: C, 68.16; H, 4.52; N, 17.48; O, 9.87.

3,6-Bis(hydroxymethyl)pyridazine (**7**).

To a mixture of 2,5-diacetoxymethylfuran (**5**) (34 g, 0.16 mole) and sodium carbonate (30 g, 0.3 mole) in methanol (200 ml), a solution of bromine (12 g, 0.15 mole) in methanol (150 ml) was slowly added at -10°, during about 1 hour. The mixture was stirred at room temperature for 1 hour. After filtration, the methanolic solution was evaporated under reduced pressure. The sodium bromide which precipitated during the concentration was then collected by filtration and the residual oil was dissolved in methanol (30 ml) and boiled for 10 minutes with acetic acid (1%, 30 ml). The solution was cooled in an ice bath and hydrazine hydrate (7.5 ml, 0.15 mole) was added wtih stirring. After heating at 50-60° for 30 minutes, the mixture was concentrated under reduced pressure and the oily residue was treated with acetone (50 ml). After evaporation of the solvent to dryness, the residue was stirred in ether for 10 minutes. The insoluble product was dissolved in methanol (50 ml) and poured in ether (500 ml) with stirring. The brown solid was collected by filtration and recrytallized from ethanol/1,2-dimethoxyethane to yield **7** (10.9 g, 52%); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 3.47 (s, 4H, 2CH$_2$), 4.78 (s, 2H, exch OH), 7.72 (s, 2H, pyridazine); ^{13}C-nmr (deuterium oxide): δ 163.7 (s, C=N), 128.2 (s, C=C), 62.8 (s, CH$_2$-OH); ms: m/z 140 (77, M$^+$), 139 (100), 111 (28), 110 (14), 109 (16), 95 (10), 94 (8), 83 (32), 82 (11), 81 (16), 80 (20), 79 (32), 65 (22), 55 (20), 53 (30), 52 (20).

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.44; H, 5.76; N, 19.99; O, 22.84. Found: C, 51.18; H, 5.86; N, 20.17; O, 22.67.

3,6-Diformylpyridazine Dioxime (**9**).

To a stirred solution of oxalyl chloride (10 ml, 0.11 mole) in methylene chloride (250 ml), dimethyl sulfoxide (17 ml, 0.22 mole) dissolved in methylene chloride (50 ml) was slowly added with cooling at -60°. The reaction mixture was stirred for 2 minutes and a solution of **8** (7 g, 0.05 mole) in methylene chloride (10 ml) with a minimum amount of dimethyl sulfoxide to dissolve the alcohol was added within 5 minutes; stirring was continued for an additional 15 minutes. Triethylamine (14 ml, 0.1 mole) was added and the reaction mixture was stirred for 5 minutes and then allowed to warm to room temperature. Water (500 ml) was then added and the aqueous layer was reextracted with additional methylene chloride (100 ml). The organic layers does not contain **9**. The aqueous layer was treated with hydroxylamine hydrochloride (14 g, 0.2 mole). A white precipitate was collected by filtatrion and washed with water. Recrystallisation from tetrahydrofuran gave **9** (7.5 g, 90%), mp >200°dec; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.80 (s, 2H, pyridazine), 8.40 (s, 2H, CH = N), 11 (br, 2H, exch OH); ms: m/z 166 (100, M$^+$), 148 (8), 123 (5), 105 (7), 91 (7), 79 (41), 63 (36), 52 (52).

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.39; H, 3.64; N, 33.73; O, 19.26. Found: C, 43.71; H, 3.40; N, 33.68; O, 19.12.

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