Pyridazine Derivatives. XIX [1]: Functionalization Studies at the 5 Position in the 6-Phenyl-3(2*H*)-pyridazinone System

Eddy Sotelo, Enrique Raviña* and Isabel Estevez

Department of Organic Chemistry, Laboratory of Medicinal Chemistry,
University of Santiago de Compostela, Santiago de
Compostela, 15706, Spain.

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A series of 6-phenyl-3(2*H*)-pyridazinones bearing different substitution at the 5 position of the pyridazinone ring were prepared in the search for new platelet aggregation inhibitors. The structure of the final compounds was determined on the basis of spectroscopics methods.

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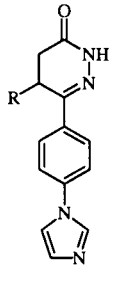
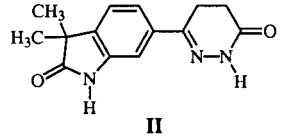
For many years digitalis glycosides have been the principal drugs used for the treatment of heart failure [2-3]. However, their use is limited by arrhythmogenic liability. The discovery of amrinone and milrinone (**VI**) led to the synthesis of a great number of agents with promise for congestive heart failure treatment in the field of nonsympathomimetic and non-glycoside agents. In this regard a considerable number of 3(2*H*)-pyridazinones and their 4,5-dihydro derivatives have attracted considerable attention in the prospect for effective agents against cardiovascular diseases [4-6]. Among these compounds, imazodan (**Ia**), CI-930 (**Ib**), indolindan (**II**), bemoradan (**III**), pimobendan (**IV**) or zardaverine (**V**) are a few examples of pyridazinones which are active as cardiotonic agents.



R = H, **Ia**
R = CH_3, **Ib**



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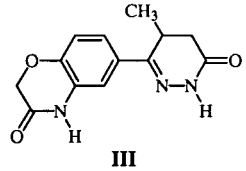
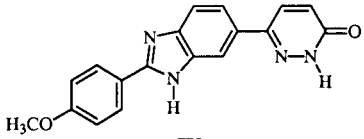


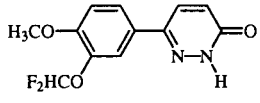
III

Figure 1.

Several years ago we began to be interested in the study of the chemistry and pharmacology of 6-aryl-3-(2*H*)-pyridazinones [7-8], in particular those substituted at the 5 position [9-12]. Recently we reported the antiplatelet aggregating activity of some 5-oxygenated pyridazinones with non c-AMP PDE-3 based mechanism and we have found that for the 6-aryl-3-(2*H*)-pyridazinones the chemical group present at the 5 position determinate their activity as antiplatelet agents [13].



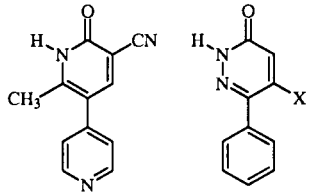
IV



V

Figure 2.

Prompted by these results, and in an attempt to establish a more detailed structure-activity relationships in this series and evaluate the modification of the pharmacological profile induced by the change at the 5 position, we continued our studies in order to obtain novel compounds bearing different substitution at 5-position of the 3-(2*H*)-pyridazinone ring.



VI

VII

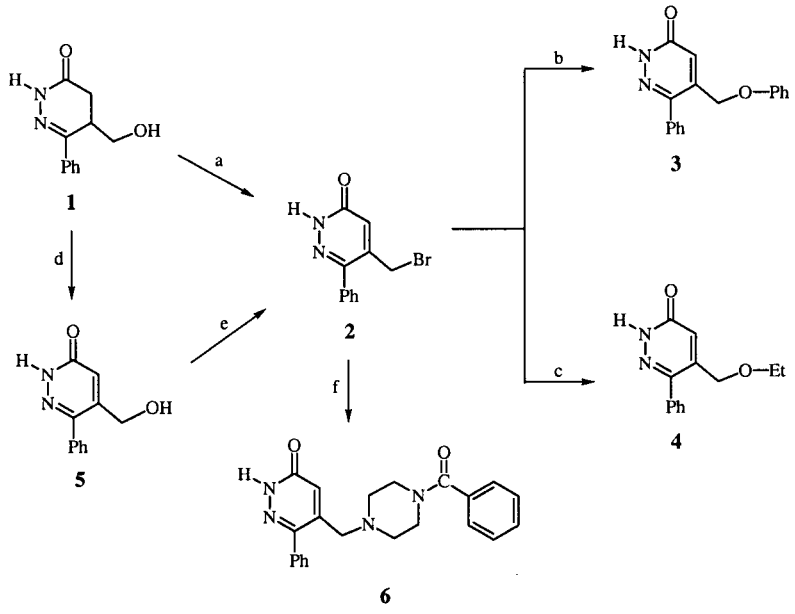
X = CHO, COOH, COOMe, OR, $CONH_2$, CN, NH_2

Figure 3.

The general synthetic strategy followed in preparation of the 5-substituted pyridazinones **VII** is outlined in the Schemes 1 and 2.

The starting material, 5-hydroxymethyl-6-phenyl-4,5-dihydro-3(2*H*)-pyridazinone, **1** is readily obtained by hydrazinolysis of β-benzoyl-γ-butyrolactone by the procedures described [14, 15]. Direct preparation of the aromatic alcohol **5** from the 4,5 dihydro derivative **1** using resublimated selenium dioxide as the oxidant gave **5** in low yield in a rather troublesome procedure. Compound **2** is obtained by two methods, heating the acetyl derivative of **1** with bromine in glacial acetic acid at 120° for 3 hours (55%), or starting from the alcohol **5**, triphenylphosphine and carbon tetrabromide in

Scheme 1



Reagents: a: Ac_2O-Py, AcOH, Br_2 100°; b: PhONa-MeOH; c: EtONa-EtOH; d: SeO_2 e: CBr_4-Ph_3P; f: $HN(CH_2)_4N$-COPh.

dichloromethane at reflux to produce the target compound **2** in high yield (90%). Attempts to obtain 5-bromomethyl derivative **2** by radical bromination of 5-methyl-6-phenyl-3(2*H*)-pyridazinone failed. Reaction of **2** with sodium ethoxide or sodium phenoxide gave the ethyl ether **3** or the phenyl ether **4**. Replacement of the bromine atom in **2** by reaction with benzoylpiperazine in methanol at room temperature gave 5-(N^4-benzoyl-N^1-piperazinylmethyl)-6-phenyl-3(2*H*)-pyridazinone **6** [16, 17].

Conversion of **1** to the aldehyde **7** was carried out in a multistep route recently described by us [13], starting from the acetate of **1** that upon aromatization, deprotection and subsequent oxidation of the 5-hydroxymethyl-6-phenyl-3(2*H*)-pyridazinone **5** with manganese dioxide afforded the aldehyde **7** in 70% overall yield. Conversion of **7** to the carboxylic acid **12** was carried out with silver oxide. 5-cyano-6-phenyl-3(2*H*)-pyridazinone **9** (Scheme 2), which can be considered structurally related to milrinone (**VI**) (1,6-dihydro-2-methyl-6-oxo-3,4'-bipyridine-4-carbonitrile), the prototype of a series of *non*-glycoside, *non*-cathecolamine cardiotonics, was alternatively obtained from the aldehyde **7** in one pot by using hydroxylamine hydrochloride and formic acid (65%) or by the dehydration of the oxime **7** with acetic anhydride (75%). Compound **9** was also directly obtained in 35% yield by nucleophilic substitution of bromine in 5-bromo-6-phenyl-3(2*H*)-pyridazinone **14** [18] using potassium cyanide in dimethyl sulfoxide at room temperature (method c). Although the reactivity of **14** toward nucleophilic reagents is low, these reactions have been extensively studied by our group and, we have found an important influence of the solvent, thus the use of polar solvents facilitate the nucleophilic substitutions in **14** in concordance with recent reports for analogous systems [19],

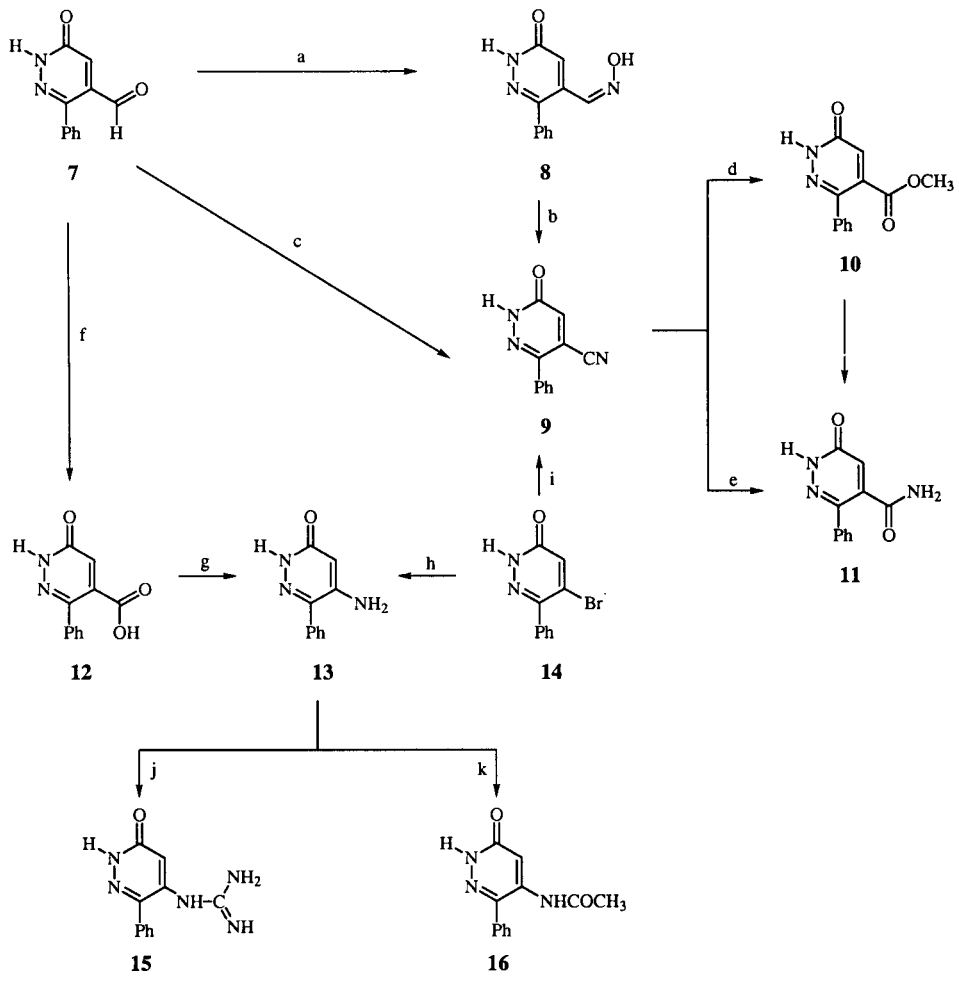
Starting from common intermediate **9**, methyl esther **10** and amide **11** were synthesized in good yields, 78 and 85%, respectively (Scheme 2). Conversion of carboxylic acid **12** into the enamine 5-amino-6-phenyl-3-(2*H*)-pyridazinone **13** was accomplished in moderate yield (45%) by Curtius rearrangement with diphenylphosphorylazide in *tert*-butyl alcohol and subsequent hydrolysis of the resulting carbamate (method a). **13** was also obtained by ammonolysis of **14** in a mixture of ammonium chloride-ammonia in a Parr reactor at high temperature and pressure (method b). Treatment of enamine **13** with methyl isothiourea in boiling ethanol permit to obtain the amidine **15**, which is a versatile intermediate for the synthesis of new pyridazinones bearing at the 5 position a heterocycle.

The structure of all compounds described herein was confirmed by analytical (Table 1) and spectroscopic data (see Experimental).

EXPERIMENTAL

Melting points were measured on a Gallemkap melting point apparatus and are uncorrected. Infrared spectra (ir) were

Scheme 2



a: NH_2OH-Py; b: Ac_2O; c: NH_2OH-HCO_2H; d: MeOH-H_2SO_4; e: H_2O_2-KOH; f: NaOH-$AgNO_3$; g: diphenylphosphoryl azide *t*-BuOH, H_2O/H^+; h: NH_4Cl-NH_3; i: NaCN-dimethyl sulfoxide; j: $NH_2CNHSCH_3$-EtOH; k: Ac_2O-EtOH.

Table 1

Physical and Analytical Data of Compounds **1-16**

Compound No.	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis % Calcd./Found C	H	N
1	81	163-164 (*i*-PrOH)	$C_{11}H_{12}N_2O_2$	64.69/64.74	5.92/5.90	13.72/13.70
2	85 [a]	181-183 (*i*-PrOH)	$C_{11}H_9BrN_2O$	49.83/50.02	3.42/3.39	10.56/10.48
3	63	139-141 (*i*-PrOH)	$C_{17}H_{14}N_2O_2$	73.36/73.41	5.07/4.95	10.07/10.15
4	55	215 (dec.) (*i*-PrOH)	$C_{13}H_{14}N_2O_2$	67.82/67.94	6.08/5.93	12.17/12.35
5	30	198-201 (EtOH)	$C_{11}H_9N_2O_2$	63.33/63.21	4.98/5.04	13.86/13.98
6	94	190-192 (EtOH)	$C_{22}H_{22}N_4O_2$	70.57/70.62	5.92/5.84	14.96/15.07
7	70	230 (*i*-PrOH)	$C_{11}H_8N_2O_2$	66.00/65.98	4.03/4.24	13.99/13.98
8	90	260-262 (*i*-PrOH)	$C_{11}H_9N_3O_2$	61.39/61.42	4.21/4.19	19.53/19.54

Table 1 (continued)

Compound No.	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis % Calcd./Found C	H	N
9	70 [a]	233-234 (*i*-PrOH)	$C_{11}H_7N_3O$	67.00/67.08	3.58/3.53	21.31/21.37
10	70	175-177 (*i*-PrOH)	$C_{12}H_{10}N_2O_3$	62.61/62.57	4.38/4.34	12.17/12.21
11	80	201-202 (*i*-PrOH)	$C_{11}H_9N_3O_2$	61.39/61.46	4.20/4.12	19.53/19.30
12	50	243-245 (*i*-PrOH)	$C_{11}H_8N_2O_3$	61.11/61.40	3.70/3.85	12.96/12.80
13	70 [a]	244 (MeOH)	$C_{10}H_9N_3O$	64.16/64.20	4.85/4.78	22.45/22.43
14	63	231 (CH_3CN)	$C_{10}H_7BrN_2O$	47.84/48.00	2.81/2.82	11.61/11.22
15	55	134-136 (*i*-PrOH)	$C_{11}H_{11}N_5O$	57.63/57.73	4.84/4.80	30.55/30.48
16	88	279-280 (*i*-PrOH)	$C_{12}H_{11}N_3O_2$	62.87/62.93	4.84/4.85	18.33/18.30

[a] = best yields of the reported methods.

recorded on a Perkin-Elmer 1640 FTIR spectrophotometer. The ^{1}H-nmr spectra were obtained on a Bruker WM250 and AM300 Hz spectrophotometer using tetramethylsilane as the internal standard (chemical shifts are in δ values, J in Hz). Mass spectra were determined on a Varian MAT-711 instrument. Elemental analyses were performed on a Perkin-Elmer 240B apparatus at the Microanalysis Service of the University of Santiago de Compostela. The progress of the reactions was monitored by thin layer chromatography with 2.5 mm Merck silica gel GF 254 strips, and the purified compounds each showed a single spot; unless otherwise stated iodine vapor and/or uv light were used for detection. Chromatographic separations were performed on a silica gel column by flash chromatography (Kieselgel 40, 0.040-0.063 mm).

4,5-Dihydro-5-hydroxymethyl-6-phenyl-3(2*H*)-pyridazinone (**1**).

This compound was prepared by a previously described procedure [11], mp 163-164°; ir (potassium bromide): 3180-3050 (NH), 1665 (CO) cm^{-1}; ^{1}H-nmr (deuteriochloroform-trifluoroacetic acid): δ 7.73 (m, 2H, aromatics), 7.48 (m, 3H, aromatics), 3.88 (m, 2H, CH_2-OH), 3.62 (m, 1H, CH), 2.95 (m, 2H, CH_2-CO).

5-Bromomethyl-6-phenyl-3(2*H*)-pyridazinone (**2**).

(Method a): To a solution of **1** (3.64 g, 17.8 mmoles) in 10 ml of dry pyridine was added acetic anhydride (3.4 ml, 36 mmoles). The resulting mixture was stirred at room temperature for 12 hours and then poured into ice-water (60 g). The acetate formed was filtered and recrystallized from ethanol, quantitative yield, mp 126-128°. To a solution of this acetate (3.5 g, 14.2 mmoles) in acetic anhydride (25 ml) was added dropwise a mixture of bromine (1.1 ml, 18 mmoles) in acetic acid and heated at 120° for 3 hours, then poured into 100 g of ice-water and neutralized with ammonium hydroxide. The 5-bromomethyl-6-phenyl-3(2*H*)-pyridazinone formed was filtered and recrystallized from 2-propanol to give 2.60 g (54%), mp 181-183°; ir (potassium bromide): 2850 (NH), 1660 (CO), 1600 (aromatics) cm^{-1}; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 13.20 (s, 1H, NH, deuterium oxide exchangeable), 7.97-7.94 (m, 2H, aromatics), 7.86-7.84 (m 3H, aromatics), 7.79 (s, 1H, CH-CO), 4.70 (s, 2H, -CH_2-Br).

(Method b): A mixture of **5** (2.5 g, 125 mmoles), carbon tetrabromide (5.18 g, mmoles) and triphenylphosphine (4.91 g, mmoles) in dichloromethane (50 ml) was heated at reflux for 20 hours under an argon atmosphere. The mixture was concentrated *in vacuo* and the oily residue was washed with acetone, the solid thus obtained was filtered and recrystallized from ethanol to give 2.85 g (85%) of **2** as white needles mp 181-183°.

5-Phenoxymethyl-6-phenyl-3(2*H*)-pyridazinone (**3**).

To a solution of sodium hydroxide (0.16 g, 3.8 mmoles) in methanol (15 ml) was added phenol (0.35 g, 3.8 mmoles), after 30 minutes a solution of **2**, (1.0 g, 3.78 mmoles) in methanol (20 ml) was added and the resulting mixture refluxed for 10 hours with continous stirring. The reaction solution was concentrated *in vacuo* and poured in ice-water, the solid thus obtained was filtered, chromatographed on silica gel (ethyl acetate-hexane 2:1) and recrystallized from methanol to provide **4** as colorless needles 0.73 g (67%), mp 139-141°; ir (potassium bromide): 2850 (NH), 1660 (CO), 1600 (aromatics) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 12.04 (s, 1H, NH deuterium oxide exchangeable), 7.50-7.46 (m, 3H, Ph), 7.40-7.35 (m, 2H, Ph), 7.20-7.15 (m, 5H, aromatics), 7.08 (s, 1H, CH-CO), 5.00 (s, 2H, CH_2-O).

5-Ethoxymethyl-6-phenyl-3(2*H*)-pyridazinone (**4**).

To a solution of sodium (0.088 g, 3.8 mmoles) in dry ethanol was added another solution of **2** (1.0 g, 3.78 mmoles) in methanol (15 ml) and this mixture was heated under reflux for 10 hours. The mixture was concentrated *in vacuo* and poured into ice-water, the solid thus obtained was filtered, chromatographed on silica gel (ethyl acetate-hexane 2:1) and recrystallized from methanol to give **4** as colorless needles 0.49 g (57%), mp 215°; ir (potassium bromide): 2850 (NH), 1660 (CO), 1600 (aromatics) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 12.45 (s, 1H, NH, deuterium oxide exchangeable), 7.50-7.43 (m, 5H, aromatics), 7.20 (s, 1H, CHCO), 4.08 (s, 2H, CH_2-O), 3.75 (q, 2H, O-CH_2-), 2.1 (t, 3H, -CH_3).

5-Hydroxymethyl-6-phenyl-3(2*H*)-pyridazinone (**5**).

A suspension of **1** (1.02 g, 5 mmoles) and resublimated selenium dioxide (1.76 g, 15 mmoles) in 30 ml of ethanol was refluxed with stirring for 1 hour. After cooling, the black precipitate formed was removed by filtration and the filtrate was evaporated *in vacuo*. The oily residue obtained was treated with 20% potassium carbonate solution (25 ml), the solid obtained was chromatographed on silica gel (ethyl acetate-hexane 1:1) and recrystallized from 2-propanol to give 0.45 g (45%) of **5** as white needles, mp 198-201°; ir (potassium bromide): 3200-2900 (NH), 1650 (CO pyridazinone), 1590 (C=C aromatics) cm^{-1}; ^{1}H-nmr (dimethyl-d_6 sulfoxide): 13.07 (s, 1H, NH, deuterium oxide exchangeable), 7.46-7.44 (m, 5H, aromatics), 6.93 (s, 1H, CHCO), 5.62 (s, 1H, OH), 4.26 (s, 2H, CH_2OH).

5-(*N*^{4}-Benzoyl-*N*^{1}-piperazinylmethyl)-6-phenyl-3(2*H*)-pyridazinone (**6**).

To a solution of *N*-benzoylpiperazine (1.3 g, 6.8 mmoles) in 10 ml of methanol was added **2** (0.9 g, 3.4 mmoles) in 10 ml of methanol. After stirring for 12 hours at room temperature, the solvent was evaporated *in vacuo* and the white solid residue was treated with water under stirring. The resulting mixture was extracted with dichloromethane (2 x 25 ml), the organics extracts were dried (sodium sulfate) and the solvent was evaporated to give 1.2 g (94%) of **6** as an oily residue which crystallized on standing, mp 190-192°; ir (potassium bromide): 3150-2900 (NH), 1660 (CO pyridazinone), 1620 (CO benzoyl-piperazine), 1600 (C=C aromatics) cm^{-1}; ^{1}H-nmr (deuteriochloroform): 13.20 (s, 1H, NH, deuterium oxide exchangeable) 7.42 (m, 5H, aromatics), 7.37 (m, 5H, aromatics), 7.18 (s, 1H, CH-CO), 3.72 (m, 2H, H_{eq}-CH-)$_2$NCO), 3.37 (m, 2H, HCH_{ax})$_2$NCO), 3.30 (s, 2H, -CH_2-), 2.40 (m, 4H, (CH_2)$_2$-NCH_2).

5-Formyl-6-phenyl-3(2*H*)-pyridazinone (**7**).

This compound was obtained from **1** in a multistep route reported by our group [13], mp 230°; ir (potassium bromide): 3180-3050 (NH), 1650 (CO) cm^{-1}; ^{1}H-nmr (deuteriochloroform-trifluoroacetic acid): δ 11.34 (br s, 1H, NH, deuterium oxide exchangeable), 8.40 (s, 1H, CHO), 7.78 (s, 1H, CH-CO), 7.56 (m, 3H, Ph), 7.46 (m, 2H, Ph).

5-Hydroxyimine-6-phenyl-3(2*H*)-pyridazinone (**8**).

A mixture of **5** (1.0 g, 5.0 mmoles), hydroxylamine hydrochloride (0.45 g, 6.5 mmoles), ethanol 15 ml, and 1.5 ml of dry pyridine was refluxed for 2 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was washed with cold water, filtered and recrystallized from ethanol to give 0.96 g (90%) of **8**, mp 260-262°; ir (potassium bromide): 3200-3000 (NH), 1688 (CO) cm^{-1}; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 12.10 (s, 1H, NH, deuterium oxide exchangeable), 7.80 (s, 1H, OH), 7.50 (m, 3H, Ph), 7.43 (m, 2H, Ph), 7.50 (s, 1H, CH-CO).

5-Cyano-6-phenyl-3(2*H*)-pyridazinone (**9**).

(Method a): A solution of **8** (0.5 g, 2.3 mmoles) in acetic anhydride (20 ml) was refluxed for 30 minutes. After cooling the mixture was made alkaline with sodium hydroxide (10%), poured onto ice and extracted with ethyl acetate. The organic extracts were dried (sodium sulfate) and the solvent was evaporated *in vacuo* to provide a solid that was recrystallized from ethanol to give 0.34 g (75%) of **9**, mp 233-234°; ir (potassium bromide): 3180-3050 (NH), 1680 (CO), 2340 (CN) cm^{-1}; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 14.03 (s, 1H, NH), 7.93 (s, 1H, CH-CO), 7.63 (m, 2H, Ph), 7.50 (m, 3H, Ph).

(Method b): A solution of **5** (1.0 g, 5.0 mmoles) and hydroxylamine hydrochloride (0.45 g, 6.5 mmoles) in formic acid (15 ml) was refluxed for 2 hours. After cooling the solution was poured onto ice and made alkaline with diluted sodium hydroxide. The resulting mixture was extracted with ethyl acetate, dried (sodium sulfate) and the solvent evaporated *in vacuo* the solid obtained was recrystallized from ethanol to give 0.55 g (65%) of **9**, mp 233-234°.

(Method c): To a solution of **13** (0.5 g, 1.9 mmoles) in 20 ml of dimethyl sulfoxide at room temperature was added, in portions, potassium cyanide (0.19 g, 2.9 mmoles). After stirring for 24 hours at room temperature, the solvent was evaporated *in vacuo*, the residue poured onto crushed ice and extracted with ethyl acetate, dried (sodium sulfate) and concentrated. The residue obtained was purified by chromatography on silica gel with ethyl acetate-hexane (1:1) as eluent to yield 0.13 g (35%) of **9**, mp 232-234°.

5-Methoxycarbonyl-6-phenyl-3(2*H*)-pyridazinone (**10**).

A solution of **9** (0.3 g, 1.5 mmoles) in methanol (10 ml), and concentrated sulphuric acid (2 ml) was refluxed for 6 hours, 1 ml of water was added and the mixture reluxed for 4 hours. After cooling this solution was poured into ice-water and the solid thus obtained was filtered and recrystallized from methanol to give 0.25 g (70%) of the esther **10**, mp 175-177°; ir (potassium bromide): 3180-3050 (NH), 1650 (CO), 1730 ($COOCH_3$) cm^{-1}; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 12.40 (s, 1H, NH), 7.89 (s, 1H, CHCO), 7.50-7.39 (m, 5H, aromatics), 3.73 (s, 3H, OCH_3).

5-Carboxamido-6-phenyl-3(2*H*)-pyridazinone (**11**).

(Method a): A mixture of **9** (0.2 g, 1.0 mmoles), ethanol (10 ml), (30%) hydrogen peroxide (5 ml) and (6*N*) potasium hydroxide (10 ml) was stirred at 10° for 2 hours and then at 40° for 3 hours. After cooling at room temperature the mixture was neutralized with sulphuric acid (5%) and extracted with ethyl acetate, dried (sodium sulfate) and concentrated to give a solid that upon recrystallization from ethanol gave 0.16 g (80%) of **11** as white solid, mp 201-202°; ir (potassium bromide): 3180-3050 (NH), 1650 (CO) cm^{-1}; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 13.50 (s, 1H, NH, deuterium oxide exchangeable), 8.20 (s, 2H, $CONH_2$), 7.60-7.45 (m, 5H, aromatics), 6.82 (s, 1H, CH-CO).

(Method b): A mixture of the esther **10** (0.31 g, 1.5 mmoles) and ammonium hydroxyde (10 ml) in methanol was refluxed for 3 hours. After cooling, the mixture was added into ice and extracted with ethyl acetate, dried (sodium sulfate) and concentrated. The residue obtained was recrystallized from ethanol to give 0.29 g of the amide **11** (90%), mp 201-202°.

5-Carboxy-6-phenyl-3(2*H*)-pyridazinone (**12**).

To a solution of the aldehyde **5** (6 g, 30 mmoles) and silver nitrate (25.5 g, 150 mmoles) in ethanol (20 ml) and water (25 ml) was stirred rapidly under an argon atmosphere, a 10% aqueous sodium hydroxide solution was added until *p*H of the reaction mixture reached 12. The resulting suspension was stirred at room temperature for 16 hours and then filtered. The filtrate was concentrated under reduced pressure, then extracted with diethyl ether. The organic solution was acidified with hydrochloric acid to *p*H 3-4 to afford a solid, which was purified by column chromatography (dichloromethane-methanol 9:1) to give 3.18 g

(50%) **12**, mp 243-245°; ir (potassium bromide): 3600 (NH), 1686 (CO pyridazinone), 1678 (CO) cm^{-1}; ^1H-nmr (dimethyl-d_6 sulfoxide): δ 12.97 (1H, br s, NH, deuterium oxide exchangeable), 7.60 (m, 2H, aromatics), 7.35 (m, 3H, aromatics), 6.53 (s, 1H, CH-CO).

5-Amino-6-phenyl-3(2*H*)-pyridazinone (**13**).

(Method a): A mixture of carboxylic acid **12** (1.0 g, 4.6 mmoles), diphenylphosphoryl azide (0.15 ml, 55.6 mmoles), triethylamine (0.60 ml), *tert*-butyl alcohol (5 ml) and dimethylformamide (10 ml) was refluxed for 36 hours, the resulting mixture was concentrated *in vacuo*, washed with a dilute solution of citric acid (15%), water and a saturated solution of sodium hydrogencarbonate. This solution was extracted with ethyl acetate, organic extracts were dried (sodium sulfate) and the solvent evaporated to give the expected carbamate (5-*tert*-butoxycarbonylamino-6-phenyl-3(2*H*)pyridazinone) which was hydrolyzed by reflux in a solution of hydrochloric acid (45%). After cooling the mixture was poured into ice-water and the amine **13** obtained was filtered and recrystallized from ethanol 0.38 g (45%), mp 244°; ir (potassium bromide): 3480-3425 (NH), 1670 (CO) cm^{-1}; ^1H-nmr (dimethyl-d_6 sulfoxide): δ 12.20 (s, 1H, NH, deuterium oxide exchangeable), 7.57 (m, 5H, aromatics), 6.05 (s, 1H, CH-CO), 3.56 (s, 2H, NH_2).

(Method b): A suspension of bromo derivative **14** [18] (0.5 g, 1.9 mmoles), ammonium chloride (0.3 g, 5.6 mmoles) and 50 ml of ammonium hydroxide was heated at 185° and a pressure of 374 psi for 3 hours in a Parr reactor. The mixture was evaporated *in vacuo* and washed with ammonium hydroxide, the solid obtained was recrystallized from ethanol to provide the amine **13**, 0.26 g (70%), mp 244°.

5-Amidino-6-phenyl-3(2*H*)-pyridazinone (**15**).

A solution of amine **13** (0.5 g, 2.6 moles) and *s*-methylisothiourea sulfate (0.40 g, 3.1 mmoles) in a 1:1 mixture of ethanol-water (25 ml) was heated at reflux for 24 hours. After cooling the mixture was concentrated and poured onto ice, the solid obtained was collected by filtration, washed with water, dried (sodium sulfate) and recrystallized from ethanol to give **15** 0.45 g (55%), mp 134-136°; ir (potassium bromide): 3200-3050 (NH), 1680 (CO) cm^{-1}; ^1H-nmr (dimethyl-d_6 sulfoxide): δ 12.60 (br s, 3H, $NHNH_2$), 7.65 (s, 1H, CH-CO), 7.63-7.39 (m, 5H, aromatics), 6.91 (br s, 1H, NH).

5-Acetylamino-6-phenyl-3(2*H*)-pyridazinone (**16**).

A mixture of amine **13** (0.5 g, 2.6 mmoles) and acetic anhydride (0.27 ml, 2.6 mmoles) was refluxed for 2 hours. After cooling the mixture was poured into ice and the precipitate obtained was collected by filtration, washed with water, dried and recrystallized from ethanol to give 0.53 g (88%) of **16**, mp 279-280°; ir (potassium bromide): 3180-3050 (NH), 1650 (CO) cm^{-1}; ^1H-nmr (dimethyl-d_6 sulfoxide): δ 13.35 (s, 1H, NH, pyridazinone), 10.00 (s, 1H, NHCO), 8.50 (s, 1H, CH-CO), 7.75 (m, 2H, Ph), 7.45 (m, 3H, Ph), 2.20 (s, 3H, $CO-CH_3$).

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