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REACTION BETWEEN 5-(PHENOXYMETHYL)-2-AMINO-2-OXAZOLINE AND N-BENZYL-3-(ETHOXYCARBONYL)-4-PIPERIDINONE HYDROCHLORIDE : A STRUCTURAL INVESTIGATION

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Abstract : The two isomeric 7-benzyl-2-(phenoxymethyl)-2,3,6,7,8,9-hexahydro-5H-[1,3]oxazolo[3,2-a] pyrido[4,3-d]pyrimidin-5-one **3** and 7-benzyl-2-(phenoxymethyl)-1,2,6,7,8,9-hexahydro-5H-[1,3]oxazolo[3,2-a]pyrido[3,4-e]pyrimidin-5-one **4** were synthesized by a one-step cyclocondensation from 5-(phenoxymethyl)-2-amino-2-oxazoline **1** with N-benzyl-3-(ethoxycarbonyl)-4-piperidinone hydrochloride **2**. Their structures were assigned by comparison of two dimensional NMR spectra (HMBC, NOESY) with the results obtained from theoretical calculations. The structure of one related hydrolysis compound was established using X-ray crystallography, allowing to further confirm the structure assignment.

Introduction

The one-step assembly of polycyclic heterocycles represents a useful strategy in organic synthesis [1]. We have reported the synthesis of a number of bicyclic heterocycles with a bridgehead nitrogen atom based on the reactivity of 2-amino-2-oxazolines with biselectrophiles [2,3]. As other cyclic amidines, the 2-amino-2-oxazolines have two competing sites for potential ring-annulation introducing regioselectivity considerations.

An empirical observation has emerged from our studies as well as those of others [4-6] which indicates that in such reactions, the endocyclic nitrogen atom is the most nucleophilic and attacks the most electrophilic carbon of the biselectrophile. A ring closure between the exocyclic nitrogen atom and the second electrophilic

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center concludes the bicyclic heterocycle synthesis. The experimental observation is supported by computational studies using semiempirical and *ab initio* calculations, which established nucleophilicity reactivity indices for the nitrogen atoms of 2-amino-2-oxazoline in relation with the partial atomic net charges [7]. Nevertheless, a second regioisomer is frequently isolated during ring-annulation, suggesting the possibility of another reaction pathway. Furthermore, rearrangement reactions can occur leading to confusing results, especially when the structure assigments are ambiguous [8].

In this work we report the one-step ring-annulation of 5-(phenoxymethyl)-2-amino-2-oxazoline **1** with N-benzyl-3-(ethoxycarbonyl)-4-piperidinone hydrochloride **2**. Under mild conditions it afforded both regioisomers, involving the endocyclic and the exocyclic nitrogen atoms of the 2-amino-2-oxazoline. As the assigment was ambiguous by usual methods, we achieved a structural study using two dimensional NMR spectrometry and ^{13}C NMR chemical shift *ab initio* calculations. Moreover, the structure of one related hydrolysis compound was established unequivocally using X-ray crystallography.

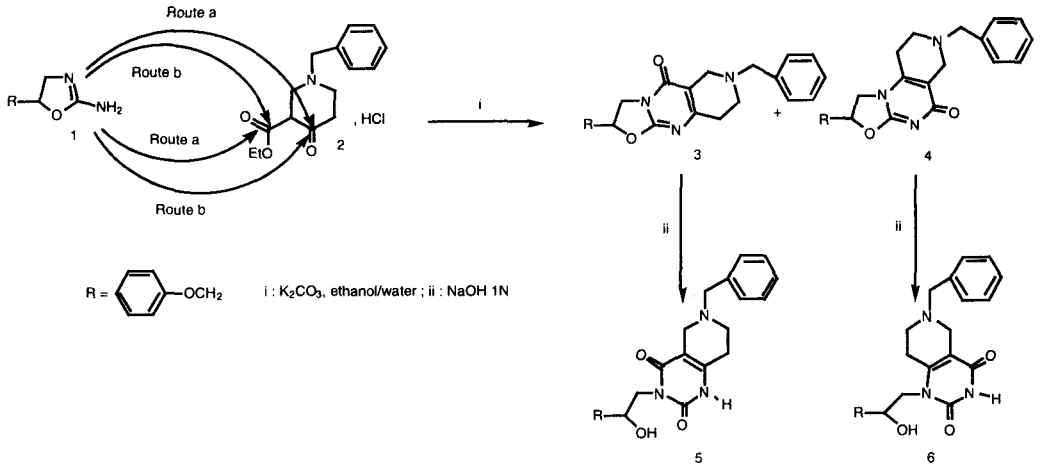
Results and discussion

The reaction of 5-(phenoxymethyl)-2-amino-2-oxazoline **1** with equimolar quantities of N-benzyl-3-(ethoxycarbonyl)-4-piperidinone hydrochloride **2** and potassium carbonate during 48 hours at 25 °C in a mixture H_2O/EtOH afforded 7-benzyl-2-(phenoxymethyl)-2,3,6,7,8,9-hexahydro-5H-[1,3]oxazolo[3,2-a] pyrido[4,3-d] pyrimidin-5-one **3** and 7-benzyl-2-(phenoxymethyl)-1,2,6,7,8,9-hexahydro-5H-[1,3]oxazolo[3,2-a]pyrido[3,4-e] pyrimidin-5-one **4** in a 1:2 ratio. By monitoring the reaction using TLC, we remarked the instantaneous formation of **3** followed by the delayed precipitation of **4**. When performed at 70°C for 4 hours, the reaction finally yielded three products **3**, **5** and **6**. TLC highlighted the quasi-simultaneous formation of **3** and **4** and their subsequent hydrolysis by opening of the oxazoline ring [3] into 6-benzyl-3-(2-hydroxy-3-phenoxypropyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione **5** and 6-benzyl-1-(2-hydroxy-3-phenoxypropyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2,4(1H,3H)-dione **6**, respectively. Finally, **3** was isolated in 20% yield whereas **4** has been used up, and **5** and **6** were isolated in a 1:1 ratio (16 % yield). The total hydrolysis of **3** or **4** achieved by heating in basic medium for 2 hours provided **5** or **6** useful as reference compounds for structural assigments.

Whatever the experimental conditions, we never observed the formation of an intermediate monosubstituted product corresponding to the sole endo nitrogen substitution. We always isolated cyclic compounds which are the result of a concerted addition. The suggested pathway for the formation of **3** and **4** via

route a and b, respectively, is depicted in scheme 1 and involves ring formation between the endocyclic and the exocyclic nitrogen atoms.

Scheme 1

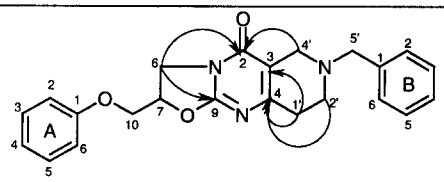


All the ^{1}H NMR chemical shifts were assigned from the COSY spectra. ^{13}C NMR chemical shifts were determined using HMQC spectra for secondary and tertiary carbons, and HMBC for quaternary carbons for both isomers **3** and **4** (Table 1).

With regard to these results, it is difficult to identify the two isomers **3** and **4**. However, the observation of the ^{13}C chemical shift values of carbons 2 and 4 are worthnoting since we can observe a large difference in the two isomers : carbon 2 is more deshielded in **4** whereas carbon 4 is more deshielded in **3**. Usual methods of ^{13}C NMR increment calculation did not give satisfactory chemical shift values. For example, using the ^{13}C NMR calculation program of ChemWindow Softshell Software the chemical shifts calculated for the carbon 4 are close to 166 ppm for **3** and 160 ppm for **4**. In the experimental spectra, a more important difference is noticed for the two isomers (160.4 and 142.8 ppm respectively).

In order to discriminate efficiently between the two isomeric formula it was decided to calculate the chemical shifts for the two compounds using *ab initio* quantum mechanics able to calculate nuclear magnetic resonance shielding tensors. Nevertheless, in order to achieve this approach it is necessary to perform calculations at a high level. For instance in the work of Cheeseman *et al.* [9] concerning derivatives of Taxol, calculations were conducted at the MP2 level using triple and quadruple-zeta basis with double polarization (TZ2P and QZ2P). In our case several attempts were performed using different bases. Finally, it was found that optimization at the Hartree-Fock level was sufficient, if one used double or triple-zeta basis. Unlike the work of Cheeseman *et al.*, the polarized basis gave less accurate results. The best results were obtained with DZ

unpolarized basis for ^{13}C and TZ unpolarized basis for ^{1}H. But in this last case, the calculated chemical shifts reached only a qualitative level and were not selected. Results for ^{13}C are summarized in Table 1. This method permitted us to assign the structures. The chemical shifts calculated by this method are close to those observed in the experimental spectra. For example one of the diagnostic carbons for the structure assignment (carbon 4) shows calculated chemical shifts of 168.88 and 146.13 ppm for compound **3** and **4** which are very close to those obtained experimentally (160.4 and 142.4 respectively). In addition, the NOESY experiments gave supplementary information : a NOE effect between proton 6 and protons 1' in isomer **4** is observed, while no correlation is observed between these two types of protons in **3**.



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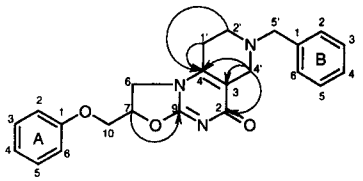

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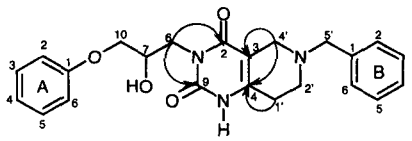
N°C	δ ^{1}H	δ ^{13}C		δ ^{1}H	δ ^{13}C	
		measured	calculated		measured	calculated
2	-	160.0	171.59	-	170.1	177.57
3	-	113.0	115.58	-	114.5	117.53
* 4	-	160.4	168.88	-	142.4	146.13
6	4.28 ; 4.35	44.4	41.17	4.23 ; 4.30	46.2	42.07
7	5.26	76.6	74.73	5.27	75.8	72.30
9	-	157.5	160.36	-	160.1	160.54
10	4.23 ; 4.34	68.0	60.86	4.29 ; 4.36	67.6	60.53
* 1'	2.66	32.6	32.11	2.62	26.2	26.30
2'	2.73	49.9	43.83	2.77	48.4	43.27
4'	3.38	49.8	42.91	3.34	50.2	43.38
5'	3.75	62.7	41.03 (Me)	3.74	62.4	40.84 (Me)
A1	-	158.4		-	158.3	
A2,6	6.94	115.0		6.95	115.0	
A3,5	7.32	128.7		7.35	128.7	
A4	7.04	122.2		7.05	122.3	
B1	-	138.8		-	138.5	
B2,6	7.38	129.4		7.39	129.4	
B3,5	7.38	130.0		7.39	130.0	
B4	7.32	127.5		7.32	127.6	

* Diagnostic carbons for structure attribution

Table 1. ^{1}H and ^{13}C chemical shifts assignments of **3** and **4**. For ^{13}C chemical shifts, the assignment deduced from the NMR data is compared with the calculated ^{13}C chemical shifts using *ab initio* quantum mechanics with DZ basis. Arrows show the ^{1}H-^{13}C long-range correlations observed using HMBC sequence.

The ^{1}H and ^{13}C NMR chemical shifts assignment of the two isomers **5** and **6** are reported in table 2. In this particular case, HMBC gave access to the structural assigment of one of two isomers since there are enough long range correlations. For isomer **6**, carbon 4 is assigned unequivocally since long range ^{1}H-^{13}C correlations are observed with protons 6, 1' and 4' whereas a sole correlation is observed between carbon 2 and protons 4', and between carbon 9 and proton 6, respectively. For isomer **5**, carbon 4 is assigned by the observation of ^{1}H-^{13}C correlations with protons 1' and 2' and not with proton 6 which in turn is correlated with carbons 2 and 9 (Table 1, Table 2).



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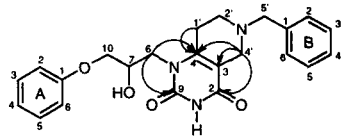


6

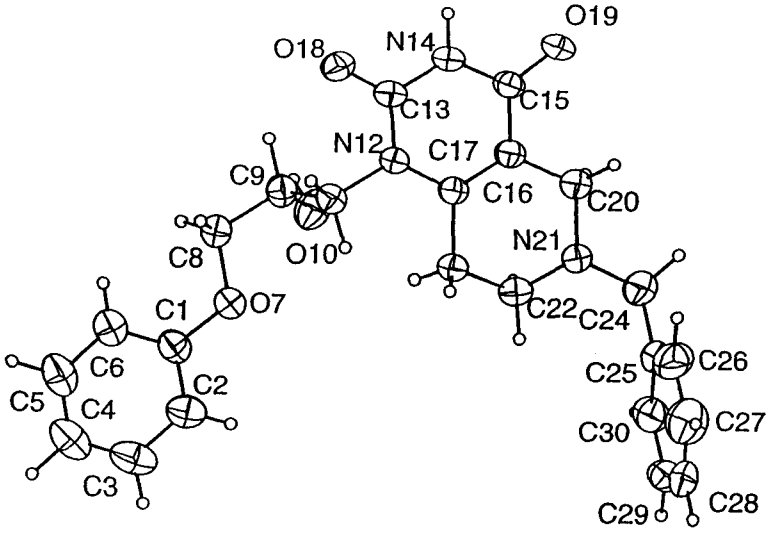
N°C	δ ^{1}H	δ ^{13}C	δ ^{1}H	δ ^{13}C
2	-	163.0	-	162.4
3	-	106.4	-	108.6
4	-	145.7	-	150.2
6	4.26	43.7	3.89 ; 4.04	47.1
7	4.26	69.1	4.31	69.2
9	-	152.8	-	152.5
10	4.04	70.0	3.98	70.0
1'	2.5	26.6	2.59;2.89	28.0
2'	2.71	48.0	2.62	49.0
4'	3.30	48.5	3.26	49.4
5'	3.73	61.8	3.61; 3.67	62.2
A1	-	152.8	-	158.7
A2,6	6.93	114.3	6.88	114.8
A3,5	7.30	129.3	7.25	129.9
A4	6.97	120.8	6.94	121.6
B1	-	137.9	-	138.2
B2,6 ; B3,5	7.4	128.2;128.9	7.30;7.31	129.4;128.7
B4	~7.3	127.2	7.26	127.6

Table 2. ^{1}H and ^{13}C chemical shifts assignment of **5** and **6**. Arrows show the ^{1}H-^{13}C long-range correlations observed using HMBC sequence.

In addition, the structure of **6** was established by X-ray crystallography (Figure 1). Bond lengths and angles show no surprising features. The Csp^2-Nsp^2 bonds in the two urea moieties [C(13)-N(12) ; C(13)-N(14) and N(14)-C(15) ; C(15)-C(16)] are slighty longer than those observed in acyclic ureas. Consequently, Csp^2-O bonds are slighty shorter as already observed in barbituric acids [10]. The pyrimidine cycle is almost planar. N(14) is in the sp^2 hybridation state as evidenced by the value of the bond angle C(13)-N(14)-C(15) = 126.43

(13)°. In the piperidine cycle, C(22) deviates from the plane along the z axis with [C(16)-C(17)-C(23)-C(22)] = -12.4 (2)° and [C(16)-C(20)-N(21)-C(22)] = 50.6 (2)°. Two hydrogen bonds occur : the first one between O(18) (x, y, z) and O(10) (2-x, -y, 1-z) with O(18).....O(10) = 2.862 (2) Å, and O(18).....H(110)-O(10) = 169.3 (2)°, the other between N(14) (x, y, z)...O(19) (2-x, -y, 2-z) with N(14)...O(19) = 2.823 (2) Å and N(14)-H(14)...O(19) = 177.2 (2)°.

Figure 1 : An ORTEP view of compound **6**



In conclusion, we reported a one-step cyclocondensation reaction between 5-(phenoxymethyl)-2-amino-2-oxazoline and the biselectrophilic N-benzyl-3-(ethoxycarbonyl)-4-piperidinone hydrochloride. Under mild conditions it afforded two isomeric tricyclic compounds through a ring-annulation involving both endocyclic and exocyclic nitrogen atoms of the 2-amino-2-oxazoline. Structure assignment of synthesized tricyclic compounds was performed by comparison of two dimensional NMR experimental spectra with results obtained from chemical shifts theoretical calculations. X-Ray crystallography was used in order to further confirm the structure assignment of one related hydrolysis compound.

EXPERIMENTAL

Microanalyses were carried out at Service Central d'Analyse CNRS, Vernaison, France. Melting points were determined with a SM-LUX-POL Leitz hot-stage microscope and were uncorrected.

NMR spectroscopy

The 1D and 2D NMR experiments were performed on a Bruker DPX400 spectrometer equipped with an inverse 5 mm broad probe at 400.13 and 100.6 MHz for ^{1}H and ^{13}C experiments, respectively. All the spectra were recorded using ca 10 mg of the compounds dissolved in 0.7 mL of CD_2Cl_2 in a 5 mm tube. ^{1}H and ^{13}C chemical shifts are given in ppm relative to the chemical shift of tetramethylsilane.

1D spectra. The ^{1}H spectra were recorded for all compounds with a spectral width of 3600 Hz, and a pulse width of 7 μs (which corresponds to a mutation angle of 90°). A scan number of 32 and an interpulse delay of 8.56 s (4.56 for the acquisition time and 4s for the relaxation delay) were used. Processing, which was done without any multiplication, was carried out with 16 K data points.

The proton decoupled ^{13}C spectra of the compounds were recorded with a spectral width of 22000 Hz with 32 K data points and a pulse width of 9.5 μs (90° mutation angle). A scan number of 200 and an interpulse delay of 2.75 s (0.75 s for the acquisition time and 2 s for the relaxation delay) were used. Exponential weighing with a line-broadening factor of 1 Hz was applied before the Fourier transform.

2D spectra. The ^{1}H-^{1}H shift correlated two dimensional COSY spectra [11] of the compounds were obtained using the COSY-90 pulse sequence. For each t1 increment, 16 scans were accumulated. The F1 and F2 spectral widths were 3600 Hz and the initial (t1,t2) matrices of 256 x 1024 real data points were zero-filled to 1024 x 1024 to give a final resolution of 3.6 Hz/points.

The ^{1}H-^{1}H NOESY experiments were recorded in the phase sensitive mode with time proportional phase incrementation [12] according to the pulse sequence of Jeener et al. [13]. The acquisition and processing parameters were the same as in the COSY experiment except that a Qsine multiplication of (2) was done in the two dimensions before the double Fourier transformation.

The one bond ^{1}H-^{13}C chemical shift correlations (HMQC) were obtained for the compounds according to the Bax sequence [14] using B_0 gradient pulses for the selection of ^{1}H coupled to ^{13}C carbons. For each t1 increment, 64 scans were accumulated. The F1 and F2 spectral widths were 21935 and 2395 Hz, respectively. The initial (t1, t2) matrices of 256 x 1024 real data points were zero-filled to 1024 x1024 to give a final resolution of 85.7 Hz/points in carbon-13 dimension (F1) and 3.6 Hz/points in the proton dimension (F2).

The ^{1}H detected heteronuclear multiple bond correlations (HMBC) were recorded using the pulse sequence proposed by Bax and Summers [15] involving a low-pass J-filter (3.8 ms) and a delay for the long range coupling (60 ms). As in the HMQC experiment, B0 gradient pulses were applied in order to select ^{1}H coupled to ^{13}C nuclei. Except for the sequence and the delays mentionned, all the parameters were the same as in the HMQC experiment.

Molecular modeling.

Molecular Mechanics. Calculations were performed on a SGI Indy 4400 SC platform running Macromodel version 5.0 (Columbia University, New-York) [16] or Insight II/Discover version 95.0/3.0.0 (M.S.I.) [17]. As calculations proved to be tedious, the general formula was simplified and the two phenyl rings A and B were omitted. Molecules were built within MacroModel, and conformational minima were found using the modified MM2* (1987 parameters) force field as implemented and completed in the MacroModel program. Built structures were minimized to a final RMS gradient 0.005 kJ.Å-1.mol-1 *via* the Truncated Newton Conjugate Gradient (TNCG) method (1000 cycles).

Quantum mechanics calculations. The MacroModel files were converted into CSSR format using an in-house program and exported toward Insight (Biosym Technologies) where TurboMole and TurboNMR calculations were performed. Geometries were optimized at the Hartree-Fock level with double and triple zeta basis without and with polarization (DZ, TZ, DZP and TZP). In these conditions the calculated chemical shift values for the TMS taken as reference were the following :

basis	^{1}H	^{13}C	^{29}Si
DZ	33.3243	205.2243	431.2854
DZP	32.0673	201.8607	396.5449
TZ	33.5691	201.5178	431.0800
TZP	32.4396	195.4747	399.3844

X-ray structure determination

Crystals of 6-benzyl-3-(2-hydroxy-3-phenoxypropyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione **5** for X-ray analysis were obtained by slow evaporation of a saturated solution of methanol/water (80/20) solution.

Crystal data. $C_{23}H_{25}N_3O_4$, M = 407.46, a well formed transparent prism of 0.35 x 0.35 x 0.10 mm was used for data collection at room temperature. Monoclinic a = 7.402 (6), b = 30.156 (3), c = 9.772 (6) Å, b = 109.49 (3)°, V = 2056 (2) $Å^3$, space group $P2_1/n$, Z = 4, D_x = 1.316 $g.cm^{-3}$, Cu-Kα (graphite monochromated), R = 0.044, S = 1.15.

Data collection and processing. Enraf-Nonius CAD-4 diffractometer using an w/2q scan mode, scan speed 6.71 deg/mn , scan width 1.8° and q in the range 2.93<q<64.94 deg. Cell parameters were determined by least-

squares fit to observed 2q values for 25 centred reflections, 2 intensity checks for one standard reflection showed no significant variation. 3496 Independent reflections were measured. (*h* 0 to 8, *k* 0 to 35, *l* -11 to 10) of which 2707 were observed $I > 2s(I)$. Lorentz and polarization (LP), extinction corrections and empirical absorption correction were applied.

Structure analysis and refinement. The structure was solved by the direct method using MULTAN 80 [18]. The C-, N-, and O-atoms were refined anisotropically. The H-atoms were placed in theoretical positions. The convergence largest D/s were < (on Bs), the highest peak in final difference was 0.442 e.Å^{-3}. The atomic coordinates were deposited within the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge CB2 IEZ, UK.

Chemistry

Cyclocondensation of 5-(phenoxymethyl)-2-amino-2-oxazoline with N-benzyl-3-(ethoxycarbonyl) -4-piperidinone hydrochloride.

A mixture of 5-(phenoxymethyl)-2-amino-2-oxazoline (4g, 0.02 mole), N-benzyl-3-(ethoxycarbonyl)-4-piperidinone hydrochloride (6g, 0.02 mole), potassium carbonate (3g, 0.022 mole) was dissolved in 100 mL of a solution of water/methanol (50/50). It was stirred at 25°C during 48 hours. Compound **3** precipitated. It was filtered off and recrystallized from methanol. The filtrate was evaporated to dryness and the residue was chromatographied on a silica gel column using chloroform/methanol (9/1) as eluant providing **4** and additionnal **3** (final yields in **3** and **4** 12 % and 26 %, respectively).

7-benzyl-2-(phenoxymethyl)-2,3,6,7,8,9-hexahydro-5H-[1,3]oxazolo[3,2-a] pyrido[4,3-d] pyrimidin-5-one **3**, mp : 159 °C ; Anal. Found : C, 70.62; H, 5.85; N, 10.58. Calc. for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.79.

7-benzyl-2-(phenoxymethyl)-1,2,6,7,8,9-hexahydro-5H-[1,3]oxazolo[3,2-a]pyrido[3,4-e] pyrimidin-5-one **4**, mp : 286 °C ; Anal. Found : C, 70.71; H, 6.06; N, 10.73. Calc. for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.79.

6-benzyl-3-(2-hydroxy-3-phenoxypropyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione 5 and 6 - benzyl - 1- (2-hydroxy-3-phenoxypropyl) -5,6,7,8-tetrahydropyrido [3,4-d] pyrimidin-2,4(1H,3H)-dione 6. A stirred solution of compound **3** or **4** (2g, 5.1 x 10^{-3} mole) and sodium hydroxide (0.21 g, 5.3 x 10^{-3} mole) in 30 mL of water was refluxed during 1 hour, then the clear solution was cooled and acidified with 1N hydrochloric acid to pH 7. The precipitate was collected by filtration, washed with water, dried and recrystallized from ethanol to provide **5** or **6**, respectively.

5 (73 %) mp : 146°C; Anal. Found : C, 67.52; H, 6.40; N, 10.26. Calc. for $C_{23}H_{25}N_3O_4$: C, 67.81; H, 6.14; N, 10.32).

6 (82 %) mp : 84°C ; Anal. Found : C, 67.66; H, 6.33; N, 10.21. Calc. for $C_{23}H_{25}N_3O_4$: C, 67.81; H, 6.14; N, 10.32).

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