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Unusual and Stereoselective Ring Closure of Unsaturated Monohydrazones with β-Ketoesters in a Solvent-Free Reaction.

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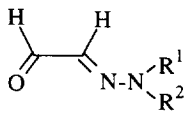
Abstract : In the presence of catalytic amounts of piperidine, the ring closure reaction of glyoxal monohydrazones **1** with several β-ketoesters **2** without solvent leads, according to the substitution of nitrogen, either to pyrrolidine nucleus fused with dihydrofuran backbone **3** (kinetically controlled product) or to functionnalized cyclohexanone **4**. Microwave irradiation converts **3** into pyridazinone **5** (thermodynamically controlled product). Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

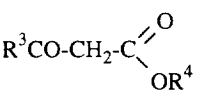
Pyridazinone derivatives are well known to exhibit pharmacological activity as hypotensive, antibacterial antiinflammatory, antitumoral and can be effective therapeutic agents for treatment of various diseases[1-4].

As part of our program to develop organic synthesis in dry media eventually under microwave irradiation[5-14], we have recently reported the synthesis of 3(2H)-pyridazinones by condensation of monophenylhydrazones of 1,2-dicarbonyl compounds with β-activated esters XCH_2CO_2R (X=CN, CO_2Me, CO_2Me, CO_2Et, $P(O)(OEt)_2$; R=Me, Et) using a new and convenient method under focused irradiation[15].

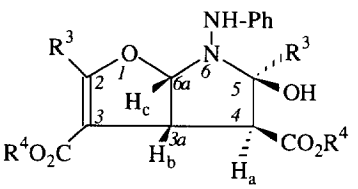
In an attempt of generalization to obtain acyl substituted pyridazinones, we now report our results concerning an unusual ring closure of glyoxal monohydrazones **1** with several β-ketoesters **2** leading to new N-substituted pyrrolidine nucleus fused with dihydrofuran backbone **3** or functionalized cyclohexanone **4**.



1a : R^1 = H, R^2 = Ph
1b : $R^1 = R^2$ = Me

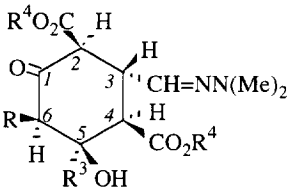


2a : $R^3 = R^4$ = Me
2b : R^3 = Me, R^4 = Et
2c : R^3 = Et, R^4 = Me
2d : R^3 = iPr, R^4 = Et
2e : R^3 = Ph, R^4 = Et



3

3aa : R^3 = Me, R^4 = Me
3ab : R^3 = Me; R^4 = Et
3ac : R^3 = Et, R^4 = Me
3ad : R^3 = iPr, R^4 = Et
3ae : R^3 = Ph, R^4 = Et

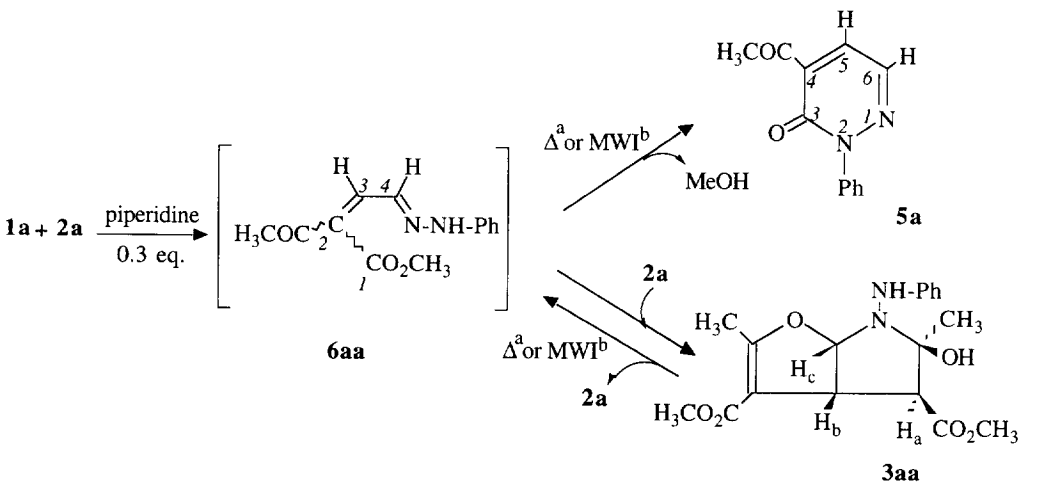


4 (R=H or Me)

4ba : R = H, R^3 = Me, R^4 = Me
4bb : R = H, R^3 = Me, R^4 = Et
4bc : R = CH_3, R^3 = Et, R^4 = Me

RESULTS AND DISCUSSION

We first studied the model reaction of monophenylhydrazone **1a** with methyl acetoacetate **2a** without solvent, in the presence of catalytic amounts of piperidine at various temperatures (Scheme 1 ; Table 1 ; Figure 1).



[a] Δ : Conventional heating

[b] MWI : Microwave irradiation

Scheme 1

Table 1.

Entry	Time (min)	T (°C)	MWI (W)	2a (eq.)	Percent[a] Completion (%)	5a[b] (%)	3aa[b] (%)
1	3	40[c]	no	1	75	33	67
2	15	40[c]	no	2	100	7	93 (89)[d]
3	3	50[e]	30	1	83	40	60
4	3	60[e]	30	1	89	63	37
5	3	70[e]	30	1	100	78	22
6	15	60[e]	30	2	100	85	15

(a) Calculated by ^{1}H NMR on the crude product and relative to major residual starting product. (b) Relative percentages (%) **5a** + (%) **3aa** = 100. (c) Approximative initial temperature. (d) Pure isolated product. (e) Temperature monitored by computer with Maxidigest MX350[16].

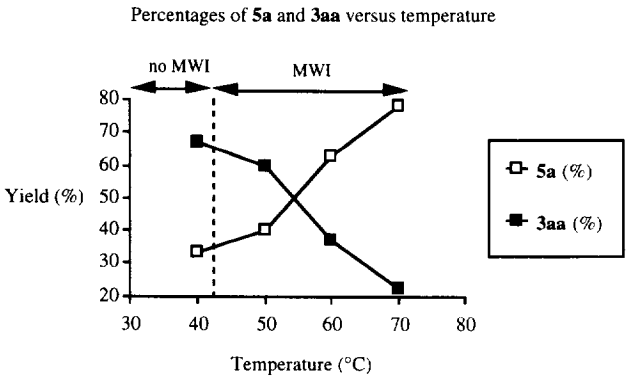


Figure 1

The results are depending on the temperature : particularly, when **1a** reacts with two equivalents of **2a** by simple mixing at room temperature (40°C results only from reaction exothermicity), a fused heterocyclic ring system containing the pyrrolidine moiety **3aa** is obtained (entry 2). To our knowledge, there is actually no report of this type of compound. The structure and the stereochemistry of **3aa** has been established by X-ray analysis (Figure 2). When the mixture of **1a** and **2a** is submitted to focused microwave irradiation (entry 5), pyridazinone **5a** is obtained (characterized by high resolution mass spectrometry (M^+ calcd : 214.0742 ; found : 214.0747). Pyridazinone **5a** is also obtained (quantitative yield) when the heterobicycle **3aa** (0.1 g) in presence of piperidine (0.02 mL) is submitted to focused microwave irradiation (4 minutes at 200W (70°C)) (Scheme 1).

If the reaction mixture is heated in an oil-bath previously set at 70°C during 4 minutes, the results are comparable : specific microwave effect can be excluded in this case.

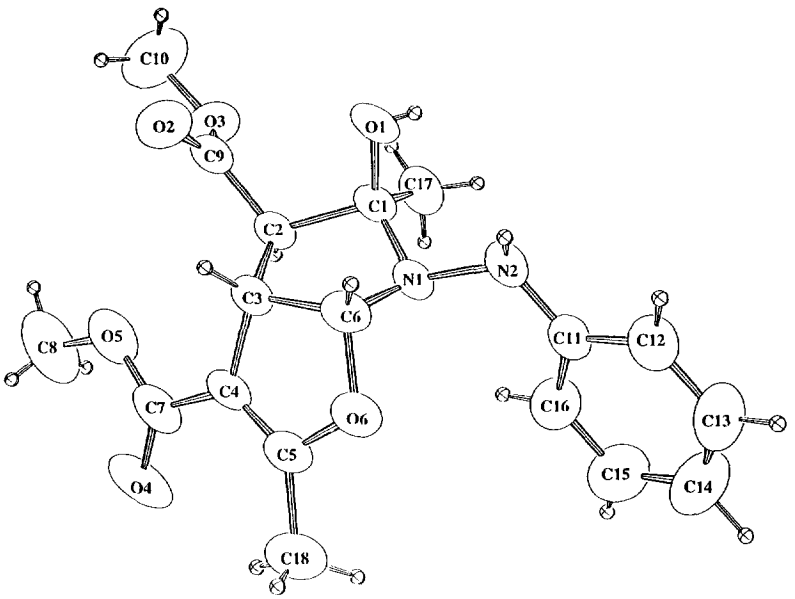


Figure 2 : Ortep diagram of compound **3aa**

Various heterobicycles **3** were prepared at room temperature or 4°C by reaction of **1a** with two equivalents of several β-ketoesters **2** (Table 2).

Table 2. Heterobicycles **3** (R^1 = H, R^2 = Ph, 2 eq. of **2** were used)

Educts	Product	R^3	R^4	T (°C)	Time	Yield %[a]
1a+2a	**3aa**	Me	Me	40[b]	15 min	89
1a+2b	**3ab**	Me	Et	40[b]	15 min	78
1a+2c	**3ac**	Et	Me	40[b]	15 min	72
1a+2d	**3ad**	iPr	Et	4	72 h	68
1a+2e	**3ae**	Ph	Et	4	24 h	37[c]

(a) Yield of isolated pure product. (b) Exothermic reaction : approximative temperature (c) Estimated by RMN ^{1}H and characterized by HRMS (M^+- H_2O calcd 496.1998 ; found 496.1969). (63% pyridazinone **5e**).

New pyridazinones were obtained with one equivalent of **2** under microwave irradiation (**5d**) or room temperature (**5e**) (Table 3).

Table 3. New Pyridazinones **5** (R^1 = H, R^2 = Ph, 1 eq. of **2** was used)

Educts	Product	R^3	R^4	MWI (T)	Time (min)	Yield %
1a+2d	**5d**	iPr	Et	30W (90°C)	20	53[a]
1a+2e	**5e**	Ph	Et	no (20°C)	15	72[b]

(a) Isolated pure product after two successive chromatographies on alumina (éluent : CH_2Cl_2/ethyl acetate 1/1 and CH_2Cl_2/petroleum ether 5/4). (b) Isolated pure product after chromatography on alumina (éluent : CH_2Cl_2/petroleum ether 8/2).

In the same way, when monodimethylhydrazone of glyoxal **1b** reacts with two equivalents of methyl acetoacetate **2a** at room temperature (1h), a novel compound **4ba** is formed (Structure established by X-ray diffraction analysis for **4bc** : Figure 3). The reaction was extended to several substituents R^3 and R^4 (Table 4). When ethyl benzoylacetate **2e** is used instead of methyl acetoacetate **2a**, the reation leads only to alkene **6be** (70% yield ; two isomers 67/33 estimated by ^1H NMR). So it may be assumed that the methylene of the acyl or propanoyl group is concerned in the cyclohexanone formation. The intermediate alkene **6bb** (R^3 = Me, R^4 = Et) has been isolated. When ethyl isobutyrylacetate **2d** reacts with **1b**, we were unable to isolate pure cyclohexanone **4bd** (only characterized by Mass Spectrometry) but the corresponding alkene **6bd** has been isolated.

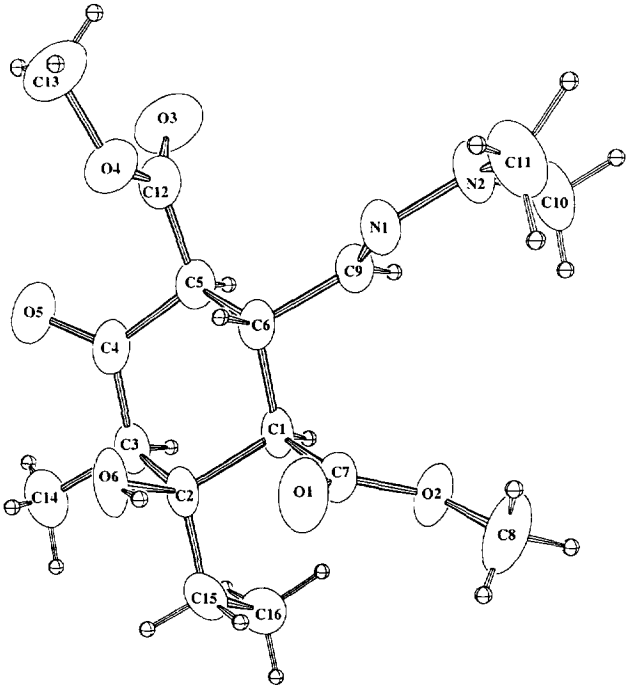
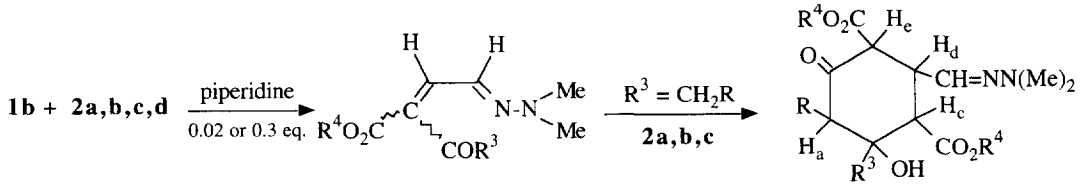


Figure 3 : Ortep diagram of compound **4bc**



6bb R^3 = Me, R^4 = Et
6bd R^3 = iPr, R^4 = Et
6be R^3 = Ph, R^4 = Et

4ba,bb R = H
4bc R = CH_3

Scheme 2

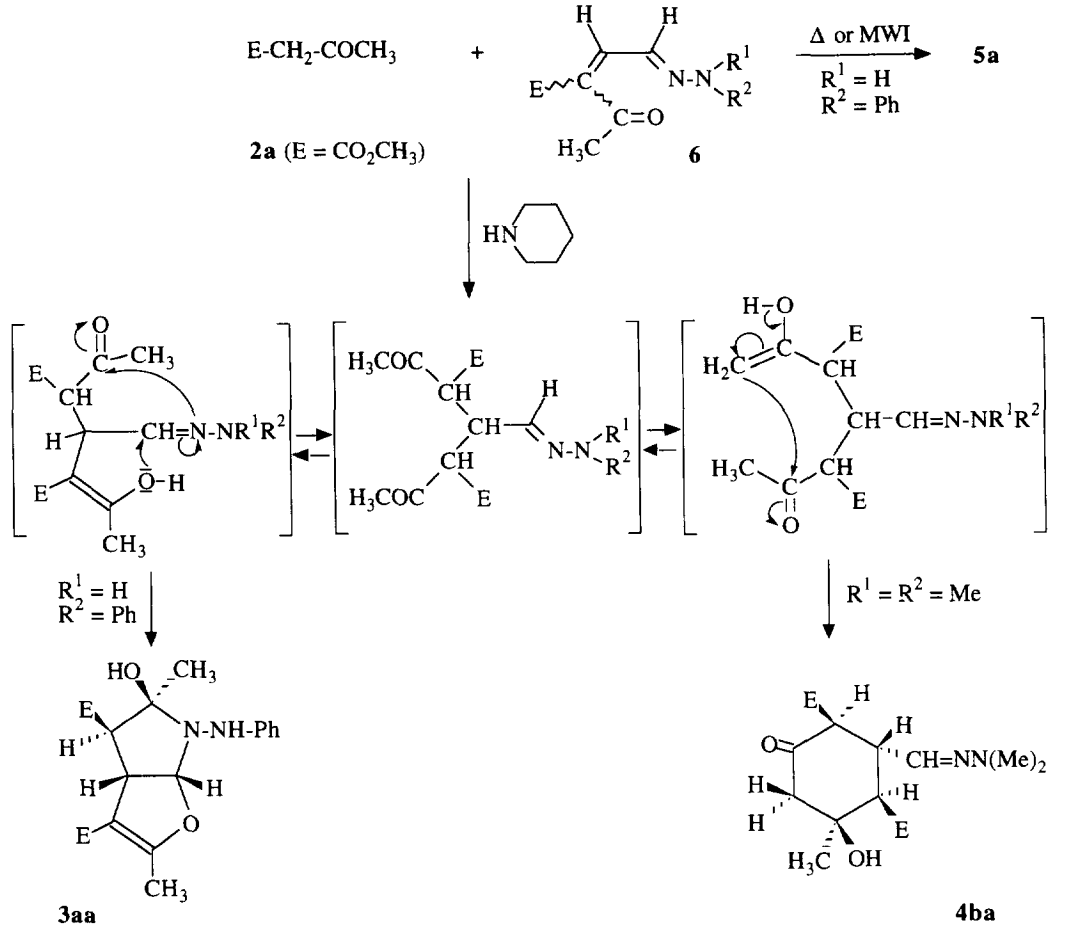
Table 4. (R^1 = R^2 = Me, T = 20°C)

Educts	Product	R^3	R^4	R	Time	Yield %[a]
1b+2a	**4ba**	Me	Me	H	1 h	54
1b+2b	**4bb**	Me	Et	H	1 h	56
	6bb	Me	Et	-	6 days	9[b]
1b+2c	**4bc**	Et	Me	Me	1 h	73
1b+2d	**6bd**	iPr	Et	-	18 h	75
1b+2e	**6be**	Ph	Et	-	18 h	70

(a) Isolated pure product. (b) 0.01 mL of piperidine instead of 0.15 mL.

The mechanism of formation of **3** could be explained by the following pathway : the first step of the reaction is the formation of the alkene **6** (eventually isolated in some cases[15]) the Z-isomer of which is transformed into pyridazinone after methanol elimination at high temperature (thermodynamically controlled product) or reacts (only E-isomer) with a second molecule of β-ketoester to afford heterobicycle **3** (kinetically controlled product) (Scheme 3) which could be converted into **5** with piperidine under microwave irradiation or conventional heating (Scheme 1) (For instance, **3ab** gave **5a** in 67% yield after 10 minutes at 100°C). It must be assumed that Z, E isomerization of alkene **6** was possible in our experimental conditions.

If the pyridazinone formation is not possible (this is the case with **1b** owing to the disubstitution of the nitrogen), cyclohexanone **4** is obtained after addition of a second molecule of β-ketoester **2** on the E-isomer of alkene **6** to give ketoenol intermediates which then cyclize to the cyclohexanone **4** in the presence of piperidine by a catalytic process. If the carbonyl group does not bear an α-hydrogen, cyclization is not possible and only alkene **6** (for example **6be**) is formed. Scheme 3 is given as an example for the formation of **3aa** and **4ba**.



Scheme 3

CONCLUSION

In summary, we have shown that the reaction of β-ketoesters with unsaturated monohydrazones can lead either to pyridazinone **5**, heterobicycle **3** or cyclohexanone **4** according to the substitution of the hydrazone nitrogen.

So we have synthesized novel heterobicycles **3** and cyclohexanones **4** by an efficient and mild method using very simple solvent-free conditions (no need for organic solvent, low temperature, very easy work-up).

The mechanism of formation of compounds **3** or **4** has been proposed : **3** appears as kinetically-controlled product and pyridazinone **5** as thermodynamically-controlled product. To our knowledge, there is no report in the literature for such ring closure of unsaturated monohydrazones during reaction with β-ketoesters.

ACKNOWLEDGEMENTS

We thank Dr Jacquault P. (Prolabo SA[17], France) for the generous gift of Maxidigest MX350 TM and Dr Perrocheau J. for helpfull discussions about NMR data. One of us (S.J) thanks Conseil Regional de Bretagne for a fellowship.

EXPERIMENTAL SECTION

General. Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a PERKIN-ELMER 157G spectrometer. ^1H NMR spectra were recorded on BRUKER WP 80 CW (80 MHz), BRUKER AC 300 P (300 MHz) spectrometers and ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a VARIAN MAT 311 at a ionizing potential of 70 eV in the Centre de Mesures Physiques de l'Ouest (CRMPO, Rennes). Elemental analyses were performed at the Laboratoire Central de Microanalyses-CNRS (Lyon). Thin-layer chromatography (TLC) were performed on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm). For preparative column chromatography, silica gel 60 Merck (230-240 Mesh ASTM) or aluminiun oxide Merck 90 (70-230 Mesh ASTM) were used. Reactions under microwave irradiation were performed into Maxidigest MX350 TM (Prolabo) microwave reactor with a single focused system. All solvents and reagents were purchased from Janssen Chimica and Aldrich Chimie and used without further purification.

Monophenylhydrazone of glyoxal **1a** or dimethylhydrazone of glyoxal **1b** were readily prepared by literature methods [18,19].

Preparation of heterobicycle 3, cyclohexanone 4, pyridazinone 5 or alkene 6.

5-hydroxy-3,4-dimethoxycarbonyl-2,5-dimethyl-6-phenylamino-3a,4,5,6a-tetrahydrofuro [2,3-b]-pyrrole (3aa).

The mixture of hydrazone **1a** (0.74 g, 5 mmol), methyl acetoacetate **2a** (1.16 g, 10 mmol) and piperidine (0.15 mL ; 0.13 g ; 0.3 eq.) was allowed to stand 15 minutes at room temperature. Washing with diethyl ether and addition of petroleum ether up to crystallization yielded **3aa** as yellow crystals (89% yield ; m.p 171°C). (Found : C, 59.69 ; H, 6.13 ; N, 7.63. $C_{18}H_{22}N_2O_6$ requires : C, 59.66 ; H, 6.12 ; N, 7.73). High-resolution MS (m/z) : Calcd for M^+-H_2O 344.1290. Found 344.1273. ^1H NMR ($CDCl_3$) δ : 1.38 (s, 3H, OH-C-$\underline{CH_3}$); 2.22 (s, 3H, H_3C-C=C); 3.07 (d, 1H, $\underline{H_a}C$-CO_2CH_3, J_{ab} = 7 Hz); 3.53 (broad s, 1H, OH); 3.67 (s, 3H, CO_2CH_3); 3.80 (s, 3H, CO_2CH_3); 4.00 (dd , 1H, $\underline{H_b}C$-CH_c, $J_{ab} \approx 7$ Hz); 5.51 (d, 1H, H_bC-$C\underline{H_c}$, J_{bc} = 8 Hz); 5.84 (broad s, 1H, NH); 6.75-7.18 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ : 14.4 (q, CH_3, $^1J_{CH}$ = 129.8 Hz); 24.6 (q, CH_3, $^1J_{CH}$ = 127.6 Hz); 44.7 (dd, $H_b\underline{C}$-CH_c, $^1J_{CH}$ = 144.3 Hz, $^2J_{CH}$ = 3.7 Hz); 50.9 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 146.6 Hz); 52.5 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 147.5 Hz); 57.8 (dd, $H_a\underline{C}$-CO_2CH_3, $^1J_{CH}$ = 139.5 Hz, $^2J_{CH}$ = 3.3 Hz); 91.9 (m, OH-$\underline{C}$-CH_3); 101.8 (d, H_bC-$\underline{C}H_c$, $^1J_{CH}$ = 172.4 Hz); 105.4 (m, C=$\underline{C}$-CO_2CH_3); 112.8-149.1 (m, C_6H_5); 165.6 (m, C=$\underline{C}$-CH_3); 168.5 (m, $\underline{C}O_2CH_3$); 172.6 (m, $\underline{C}O_2CH_3$).

X-Ray Crystallographic Analysis Data for 3aa : $C_{18}H_{22}O_6N_2$.

Crystal data for $C_{18}H_{22}O_6N_2$ (**3aa**), Mr = 362.39, triclinic, p-1, a = 9.283(8), b = 10.396(2), c = 10.888(9)Å, α = 89.17(4), β = 66.02(7), γ = 85.01(3)°, V = 956(2)Å^{-3}, Z = 2, D_x = 1.259 Mg.m^{-3}, λ(MoKα) = 0.70926Å, μ = 0.89 cm^{-1}, F(000) = 384, T = 293 K, final R = 0.045 for 2244 observations. The sample (0.35*0.35*0.45 mm) is studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections.

The data collection ($2\theta_{max}$ = 50°, scan $\omega/2\theta$ = 1, t_{max} = 60 s, range HKL : H 0,11 K -12,12 L -11,11, intensity controls without appreciable decay (0.2%) gives 3487 reflections from which 2244 independant (R_{int} = 0.012) with I>5σ(I). After Lorenz and polarization corrections the structure was solved with Direct Method which reveals all the non-hydrogen atoms of the structure. After isotropic (R = 0.105), then anisotropic refinement (R = 0.085), all the hydrogen atoms are found with a Fourier Difference between 0.73 and 0.25 e.Å^{-3}. The whole structure was refined by the full-matrix least-square techniques (use of F magnitude ; x, y, z, β_{ij} for N, O and C atoms and x, y, z for H atoms ; 302 variables and 2244 observations ; w = $1/\sigma(F_o)^2=[\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R = 0.048, R_w = 0.045 and S_w = 0.85 (residual $\Delta\rho \leq$ 0.19 e Å^{-3}). Atomic scattering factors from International Tables for X-ray Crystallography (1974)[20]. All the calculations were performed on a Digital MicroVAX3100 computer with the MOLEN package[21]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

5-hydroxy-3,4-diethoxycarbonyl-2,5-dimethyl-6-phenylamino-3a,4,5,6a-tetrahydrofuro [2,3-b]-pyrrole (3ab).

This compound was prepared from the mixture of the hydrazone **1a** (0.74 g, 5 mmol), ethyl acetoacetate **2b** (1.30 g, 10 mmol) and piperidine (0.15 mL ; 0.13 g ; 0.3 eq.) after standing 15 minutes at room temperature. Washing with diethyl ether gave **3ab** (78% yield ; m.p 149°C). (Found : C, 61.69 ; H, 6.83 ; N, 6.99. $C_{20}H_{26}N_2O_6$ requires : C, 61.53 ; H, 6.71 ; N, 7.17). High-resolution MS (m/z) : Calcd for M^+-H_2O 372.1681. Found 372.1685. ^{1}H NMR ($CDCl_3$) δ : 1.24 (t, 3H, $CO_2CH_2\underline{CH_3}$); 1.32 (t, 3H, $CO_2CH_2\underline{CH_3}$); 1.40 (s, 3H, OH-C-$\underline{CH_3}$); 2.24 (s, 3H, C=C-CH_3); 3.09 (d, 1H, $\underline{H_a}$-C-$CO_2C_2H_5$, J_{ab} = 7 Hz); 3.31 (broad s, 1H, OH); 4.03 (dd, 1H, $\underline{H_b}$C-CH_c, $J_{ab} \approx$ 7 Hz); 4.13-4.31 (m, 4H, $2CO_2\underline{CH_2}CH_3$); 5.50 (d, 1H, H_bC-$C\underline{H_c}$, J_{bc} = 8 Hz); 5.79 (broad s, 1H, NH); 6.78-7.26 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ : 14.2 (2 superposed qt , $2CO_2CH_2\underline{C}H_3$, $^1J_{CH}$ = 127 Hz, $^2J_{CH}$ = 2.6 Hz); 14.4 (q, CH_3, $^1J_{CH}$ = 129.8 Hz); 24.7 (q, CH_3, $^1J_{CH}$ = 127.6 Hz); 44.3 (dd, $H_b\underline{C}$-CH_c, $^1J_{CH}$ = 144.9 Hz, $^2J_{CH}$ = 4.2 Hz); 57.9 (dm, $H_a\underline{C}$-$CO_2CH_2CH_3$, $^1J_{CH}$ = 136 Hz); 59.7 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 146.5 Hz, $^2J_{CH}$ = 4.4 Hz); 61.5 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 145.7 Hz, $^2J_{CH}$ = 4.5 Hz); 91.8 (m, OH-$\underline{C}$-CH_3); 101.6 (d, H_bC-$\underline{C}H_c$, $^1J_{CH}$ = 172 Hz); 105.7 (m, C=$\underline{C}$-$CO_2CH_2CH_3$); 112.9-149.1 (m, C_6H_5); 165.2 (m, C=$\underline{C}$-CH_3); 168.3 (m, $\underline{C}O_2CH_2CH_3$); 171.9 (m, $\underline{C}O_2CH_2CH_3$).

5-hydroxy-3,4-dimethoxycarbonyl-2,5-diethyl-6-phenylamino-3a,4,5,6a-tetrahydrofuro-[2,3-b]-pyrrole (3ac)

The procedure used was the same as for compound **3ab** using methyl 3-oxopentanoate **2c** instead of **2b** (1.30g, 10 mmol). (72% yield ; m.p 164°C). (Found : C, 61.57 ; H, 6.55 ; N, 7.22. $C_{20}H_{26}N_2O_6$ requires : C, 61.53 ; H, 6.71 ; N, 7.17). High-resolution MS (m/z) : Calcd M^+ 390.1790. Found 390.1784. ^{1}H NMR ($CDCl_3$) δ : 0.80 (t, 3H, C=C-$CH_2\underline{CH_3}$); 1.16 (t, 3H, OH-C-CH_2-$\underline{CH_3}$); 1.68 (q, 2H, C=C-$\underline{CH_2}CH_3$); 2.61 (sext, 1H, OH-C-$H_A\underline{C}H_B$-CH_3); 2.80 (sext, 1H, OH-C-$\underline{H_A}CH_B$-CH_3); 3.07 (d, 1H, $\underline{H_a}$-C-CO_2CH_3, J_{ab} = 7 Hz); 3.68 (s, 3H, CO_2CH_3); 3.80 (broad s, 4H, CO_2CH_3 et OH); 3.95 (dd, 1H, $\underline{H_b}$C-CH_c, $J_{ab} \approx$ 7 Hz); 5.55 (d, 1H, H_bC-$C\underline{H_c}$, J_{bc} = 8 Hz); 5.84 (broad s, 1H, NH); 6.77-7.18 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ : 8.6 (qt, $CH_2\underline{C}H_3$, $^1J_{CH}$ = 126.3 Hz, $^2J_{CH}$ = 4.2 Hz); 11.1 (qt, $CH_2\underline{C}H_3$, $^1J_{CH}$ = 128.8 Hz, $^2J_{CH}$ = 5.1 Hz); 21.4 (tq, $\underline{C}H_2CH_3$, $^1J_{CH}$ = 130.2 Hz, $^2J_{CH}$ = 4.5 Hz); 29.6 (tq, $\underline{C}H_2CH_3$, $^1J_{CH}$ = 126.6 Hz); 45.7 (dd, $H_b\underline{C}$-CH_c, $^1J_{CH}$ = 144.7 Hz, $^2J_{CH}$ = 4.2 Hz); 50.9 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 146.5 Hz); 52.5 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 147.5 Hz); 54.3 (dq, H_a-$\underline{C}$-CO_2CH_3, $^1J_{CH}$ = 137 Hz, $^2J_{CH}$ = 3.3 Hz); 94.8 (m, OH-$\underline{C}$-C_2H_5); 102.9 (d, H_bC-$\underline{C}$-H_c, $^1J_{CH}$ = 172.1 Hz); 104.1 (m, C=$\underline{C}$-CO_2CH_3); 113.1-148.7 (m, C_6H_5); 165.4 (m, C=$\underline{C}$-C_2H_5); 173.3 (m, $\underline{C}O_2CH_3$); 174 (m, $\underline{C}O_2CH_3$).

5-hydroxy-3,4-diethoxycarbonyl-2,5-diisopropyl-6-phenylamino-3a,4,5,6a-tetrahydrofuro [2,3-b]-pyrrole (3ad)

This compound was obtained after 72 hours at 4°C from **1a** (0.74g, 5 mmol) and ethyl isobutyrylacetate (1.58g, 10 mmol). Washing with diethyl ether and addition of petroleum ether up to crystallization gave **3ad** (68% yield ; m.p 130°C). (Found : C, 64.85 ; H, 7.80 ; N, 6.21. $C_{24}H_{34}N_2O_6$ requires C, 64.55 ; H, 7.67 ; N, 6.27). High-resolution MS (m/z) : Calcd M^+ 446.2417. Found 446.2375. ^1H NMR ($CDCl_3$) δ : 0.86 (d, 3H, OH-C-CH($\underline{CH_3}$)$_2$, J_{HH} = 7.2 Hz); 0.89 (d, 3H, OC-CH($\underline{CH_3}$)$_2$, J_{HH} = 6.9 Hz); 1.1 (d, 3H, OC-CH($\underline{CH_3}$)$_2$, J_{HH} = 6.9 Hz); 1.22 (d, 3H, OH-C-CH($\underline{CH_3}$)$_2$, J_{HH} = 7.1 Hz); 1.25 (t, 3H, $CO_2CH_2\underline{CH_3}$); 1.32 (t, 3H, $CO_2CH_2\underline{CH_3}$); 2.06 (heptuplet, 1H, OH-C-CH($\underline{CH_3}$)$_2$, J_{HH} = 7.1 Hz); 3.04 (d, 1H, $\underline{H_a}$-C-$CO_2C_2H_5$, J_{ab} = 7.5 Hz); 3.67 (heptuplet, 1H, OC-CH($\underline{CH_3}$)$_2$, J_{HH} = 6.9 Hz); 3.88 (dd, 1H, $\underline{H_b}$C-CH_c, $J_{ab} \approx$ 7.5 Hz); 4.20 (2 complex q, 4H, $2CO_2\underline{CH_2}CH_3$); 4.36 (broad s, 1H, OH); 5.55 (d, 1H, H_bC-$C\underline{H_c}$, J_{bc} = 8.5 Hz); 5.9 (broad s, 1H, NH); 6.7-7.18 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$) δ : 13.9 (qt, $CO_2CH_2\underline{C}H_3$, $^1J_{CH}$ = 127.2 Hz, $^2J_{CH}$ = 2.5 Hz); 14.4 (qt, $CO_2CH_2\underline{C}H_3$, $^1J_{CH}$ = 126.7 Hz, $^2J_{CH}$ = 2.5 Hz); 16.9 (qm, CH($\underline{C}H_3$)$_2$, $^1J_{CH}$ = 126 Hz, $^2J_{CH}$ = 5 Hz); 18.1 (qm, CH($\underline{C}H_3$)$_2$, $^1J_{CH}$ = 126 Hz, $^2J_{CH}$ = 4.9 Hz); 19.51 et 19.54 (qm broad, CH($\underline{C}H_3$)$_2$, $^1J_{CH}$ = 128 Hz, $^2J_{CH}$ = 5.6 Hz); 26.9 (dm, $\underline{C}H(CH_3)_2$, $^1J_{CH}$ = 133.4 Hz, $^2J_{CH}$ = 4 Hz); 33 (dm, $\underline{C}H(CH_3)_2$, $^1J_{CH}$ = 128.4 Hz); 46.6 (dd, $H_b\underline{C}$-CH_c, $^1J_{CH}$ = 144.2 Hz, $^2J_{CH}$ = 4.1 Hz); 51.4 (dm, $H_a\underline{C}$-$CO_2CH_2CH_3$, $^1J_{CH}$ = 137.9 Hz); 59.5 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 147 Hz, $^2J_{CH}$ = 4.3 Hz); 61.7 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 147.9 Hz, $^2J_{CH}$ = 4.4 Hz); 97.1 (m, OH-$\underline{C}$-CH(CH_3)$_2$); 103.1 (m, C=$\underline{C}$-$CO_2CH_2CH_3$); 103.9 (d, H_bC-$\underline{C}H_c$, $^1J_{CH}$ = 171.9 Hz); 113.3-148.3 (m, C_6H_5); 165 (m, C=$\underline{C}$-CH(CH_3)$_2$); 175 (m, $\underline{C}O_2CH_2CH_3$); 176.1 (m, $\underline{C}O_2CH_2CH_3$).

5-hydroxy-2,4-dimethoxycarbonyl-3-(dimethylhydrazonomethyl)-5-methyl-cyclohexan-1-one (4ba)

This compound was prepared from **1b** (0.5g, 5 mmol) and **2a** (1.16g, 10 mmol) as described for compound **3aa** during 1 hour at room temperature (54% yield ; m.p : 128°C). (Found : C, 53.67 ; H, 7.19 ; N, 8.98. $C_{14}H_{22}N_2O_6$ requires C, 53.49 ; H, 7.05 ; N, 8.91). High-resolution MS (m/z) : Calcd M^+ 314.14777. Found 314.14764. ^1H NMR ($CDCl_3$) δ : 1.31 (s, 3H, OH-C-$\underline{CH_3}$); 2.45 (d, 1H, $^1J_{HH}$ = 14.1 Hz); 2.61 (d, 1H, $^2J_{HH}$ = 14.1 Hz); 2.70 (s, 6H, N(Me)$_2$); 2.89 (d, 1H, $^3J_{HH}$ = 12 Hz); 3.35 (broad s, 1H, OH); 3.62 (d, 1H, $^3J_{HH}$ = 12 Hz); 3.69 (d, 1H, $^3J_{HH}$ = 3.8 Hz); 3.73 (s, 3H, CO_2CH_3); 3.77 (s, 3H, CO_2CH_3); 6.39 (d, 1H, $^3J_{HH}$ = 3.8 Hz). ^{13}C NMR ($CDCl_3$) δ : 28.4 (q, OH-C-$\underline{C}H_3$, $^1J_{CH}$ = 126.6 Hz); 41.5 (dm, $H_d\underline{C}$-CH_c, $^1J_{CH}$ = 138.3 Hz, $^2J_{CH}$ = 4.4 Hz); 42.8 (qq, N-N(CH_3)$_2$, $^1J_{CH}$ = 135.6 Hz, $^3J_{CH}$ = 3.9 Hz); 52.06 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 147.2 Hz); 52.02 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 147.7 Hz); 52.8 (tm, $\underline{C}H_A$); 54.8 (dm, H_dC-$\underline{C}H_c$, $^1J_{CH}$ = 132.6 Hz); 59.6 (dm, $H_e\underline{C}$-C=O, $^1J_{CH}$ = 133.8 Hz, $^2J_{CH}$ = 2.44 Hz); 72.9 (m quadruplet aspect, OH-$\underline{C}$-CH_3); 131.8 (dm, $H_X\underline{C}$=NN(Me)$_2$, $^1J_{CH}$ = 167.2 Hz); 169.1 (m, $\underline{C}O_2CH_3$); 174.4 (m, $\underline{C}O_2CH_3$); 202.2 (m, H_3CO_2C-C-$\underline{C}$=O). As selective irradiations did not allow to establish clearly the molecular structure, chemical shifts (^1H and ^{13}C) have been determined in C_6D_6. ^1H NMR (C_6D_6) δ : 0.96 (s, 3H, OH-C-$\underline{CH_3}$); 1.71 and 2.46 (AB system, $^2J_{AB}$ = 14 Hz); 2.41 (s, 6H, N(Me)$_2$); 2.47 (s, 1H, OH); 2.56 (d, 1H, $\underline{H_c}$-C-CO_2Me, $^3J_{HH}$ = 12 Hz); 3.30 (s, 3H, CO_2CH_3); 3.49 (s, 3H, CO_2CH_3); 3.59 (d, 1H, $\underline{H_e}$-C-C=O, $^3J_{HH}$ = 12.2 Hz); 4.04 (td, 1H, $\underline{H_d}$C-CH=N, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 4.2 Hz); 6.35 (d, 1H, H-C=N, $^3J_{HH}$ = 4.2 Hz). ^{13}C NMR (C_6D_6) δ : 28.7 (q, OH-C-$\underline{C}H_3$); 42 (dm, $H_d\underline{C}$-CH_c); 42.8 (qq, N-N(CH_3)$_2$); 51.7 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 144.5 Hz); 52 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 147.1 Hz); 53.1 (tm, $\underline{C}H_A$); 55.3 (dm, H_dC-$\underline{C}H_c$); 60.3 (dm, $H_e\underline{C}$-C=O); 73.1 (m, OH-$\underline{C}$-CH_3); 132.6 (dm, H$\underline{C}$=NN(Me)$_2$, $^1J_{CH}$ = 165 Hz); 169 (m, $\underline{C}O_2CH_3$); 174.7 (m, $\underline{C}O_2CH_3$); 202 (m, H_3CO_2C-C-$\underline{C}$=O).

5-hydroxy-2,4-diethoxycarbonyl-3-(dimethylhydrazonomethyl)-5-methyl-cyclohexan-1-one (4bb)

The procedure was the same as for compound **4ba** using **2b** (1.30g, 10 mmol) instead of **2a**. (56% yield ; m.p 113°C). (Found : C, 56.35 ; H, 7.64 ; N, 8.15. $C_{16}H_{26}N_2O_6$ requires C, 56.13 ; H, 7.65 ; N, 8.18). High-resolution MS (m/z) : Calcd M^+ 342.17907. Found 342.17883. ^1H NMR ($CDCl_3$) δ : 1.23-1.31 (2t, 6H, 2 $CO_2CH_2\underline{C}H_3$); 1.32 (s, 3H, OH-C-$\underline{C}H_3$); 2.42 and 2.61 (AB system, $^2J_{AB}$ = 14 Hz, $^4J_{HH}$ = 2 Hz); 2.71 (s, 6H, $N(Me)_2$); 2.86 (d, 1H, $\underline{H}_c$-C-CO_2Et, $^3J_{HH}$ = 11.7 Hz); 3.44 (d, 1H, OH, $^4J_{HH}$ = 2 Hz); 3.60 (d, 1H, H_eC-C=O, $^3J_{HH}$ = 12.2 Hz); 3.73 (td, 1H, H_dC-CH=N, $^3J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 3.4 Hz); 4.24 (2q, 4H, 2 $CO_2\underline{C}H_2CH_3$); 6.41 (d, 1H, H-C=N, $^3J_{HH}$ = 3.9 Hz). ^{13}C NMR ($CDCl_3$) δ : 14.25 (qt, $CO_2CH_2\underline{C}H_3$, $^1J_{CH}$ = 127.9 Hz); 14.3 (qt, $CO_2CH_2\underline{C}H_3$, $^1J_{CH}$ = 127.2 Hz); 28.4 (qd, OH-C-$\underline{C}H_3$, $^1J_{CH}$ = 126.7 Hz); 41.6 (dm, $H_d\underline{C}$-CH_c, $^1J_{CH}$ = 138.2 Hz, $^2J_{CH}$ = 6.5 Hz); 42.7 (qq, $N(Me)_2$, $^1J_{CH}$ = 135.5 Hz, $^2J_{CH}$ = 3.96 Hz); 52.9 (tm, $\underline{C}H_A$, $^1J_{CH}$ = 130 Hz, $^2J_{CH}$ = 3.7 Hz); 54.8 (dm, H_dC-$\underline{C}H_c$, $^1J_{CH}$ = 134.2 Hz); 59.7 (dm, $H_e\underline{C}$-C=O, $^1J_{CH}$ = 130.5 Hz); 61 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 147.6 Hz, $^2J_{CH}$ = 4.5 Hz); 61.3 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 148.2 Hz, $^2J_{CH}$ = 4.4 Hz); 73 (m, OH-$\underline{C}$-CH_3); 131.7 (dm, $H\underline{C}$=NN$(Me)_2$, $^1J_{CH}$ = 162 Hz); 168.5 (m, $\underline{C}O_2CH_2CH_3$); 174.1 (m, $\underline{C}O_2CH_2CH_3$); 202.2 (m, EtO_2C-C-$\underline{C}$=O).

5-hydroxy-2,4-dimethoxycarbonyl-3-(dimethylhydrazonomethyl)-5-ethyl-6-methyl-cyclohexan-1-one (4bc)

The procedure was the same as for compound **4ba** : **2c** (1.30g, 10 mmol) replaced **2a**. (73% yield ; m.p 146°C). (Found : C, 56.38 ; H, 7.72 ; N, 8.24. $C_{16}H_{26}N_2O_6$ requires C, 56.13 ; H, 7.65 ; N, 8.18). High-resolution MS (m/z) : Calcd M^+ 342.17907. Found 342.17956. ^1H NMR ($CDCl_3$) δ : 0.95 (t, 3H, $CH_2\underline{C}H_3$); 1.08 (d, 3H, H-C-$\underline{C}H_3$); 1.32 (sext, 1H, $\underline{H}_A$·CH_B·CH_3); 1.79 (sext, 1H, H_A·$C\underline{H}_B$·CH_3); 2.57 (q, 1H, $\underline{H}$-C-CH_3); 2.7 (s, 6H, $N(Me)_2$); 3.1 (broad d, 2H, 1H + OH, $^3J_{HH}$ = 11.5 Hz); 3.64 (d, 1H, $^3J_{HH}$ = 12.4 Hz); 3.68-3.76 (2 broad s, 8H, 2 CO_2CH_3 + 2H); 6.39 (d, 1H, N=C-$\underline{H}$). ^{13}C NMR ($CDCl_3$) δ : 6.7 (qd, H-C-$\underline{C}H_3$, $^1J_{CH}$ = 128.4 Hz, $^2J_{CH}$ = 4 Hz); 9 (qt, $CH_2\underline{C}H_3$, $^1J_{CH}$ = 125.8 Hz, $^2J_{CH}$ = 4.15 Hz); 31.4 (tq, $\underline{C}H_2CH_3$, $^1J_{CH}$ = 129.2 Hz, $^2J_{CH}$ = 3.6 Hz); 41.3 (dm, $H_d\underline{C}$-CH_c, $^1J_{CH}$ = 138.5 Hz, $^2J_{CH}$ = 5.2 Hz); 42.7 (qq, $N(Me)_2$, $^1J_{CH}$ = 135.5 Hz, $^3J_{CH}$ = 3.7 Hz); 49.4 (dm, H-$\underline{C}$-CH_3, $^1J_{CH}$ = 123.1 Hz); 52 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 147.4 Hz); 52.3 (dm, H_dC-$\underline{C}H_c$, $^1J_{CH}$ = 131.9 Hz, $^2J_{CH}$ = 4.2 Hz); 59.4 (dm, $H_e\underline{C}$-C=O, $^1J_{CH}$ = 131.7 Hz, $^2J_{CH}$ = 6 Hz); 78 (m, OH-$\underline{C}$-C_2H_5); 132.1 (dm, H$\underline{C}$=NN$(Me)_2$, $^1J_{CH}$ = 159.8 Hz); 169.2 (m, $\underline{C}O_2CH_3$); 174.4 (m, $\underline{C}O_2CH_3$); 204.7 (m, MeO_2C-C-$\underline{C}$=O). As ^{13}C NMR spectra in $CDCl_3$ did not reveal the presence of another carbon of methoxycarbonyl group and ^1H NMR spectra in $CDCl_3$ did not allow the assignement of all hydrogens, we have recorded NMR spectra (^{13}C and ^1H) with samples diluted with C_6D_6. ^1H NMR (C_6D_6) δ : 0.61 (t, 3H, $CH_2\underline{C}H_3$, $^3J_{HH}$ = 7.6 Hz); 1.08 (d, 1H, H-C-$\underline{C}H_3$, $^3J_{HH}$ = 6.6 Hz); 1.15 (sext, 1H, $\underline{H}_A$·CH_B·CH_3, $^3J_{HH}$ = 7.4 Hz); 1.59 (sext, 1H, H_A·$C\underline{H}_B$·CH_3, $^3J_{HH}$ = 7.6 Hz); 1.9 (broad q, 1H, $\underline{H}$-C-CH_3, $^3J_{HH}$ = 6.5 Hz); 2.4 (s, 6H, $NN(Me)_2$); 2.91 (d, 1H, $\underline{H}_c$-C-CO_2Me, $^3J_{HH}$ = 12 Hz); 3.1 (d, 1H, OH, $^4J_{HH}$ = 1.5 Hz); 3.24 (s, 3H, CO_2CH_3); 3.5 (s, 3H, CO_2CH_3); 3.64 (d, 1H, $\underline{H}_eC$-C=O, $^3J_{HH}$ = 12.4 Hz); 4.09 (td, 1H, $\underline{H}_dC$-CH=N , $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 4.2 Hz); 6.35 (d, 1H, $\underline{H}$C=NN$(Me)_2$, $^3J_{HH}$ = 4.2 Hz). ^{13}C NMR (C_6D_6) δ : 7.4 (qd, H-C-$\underline{C}H_3$, $^1J_{CH}$ = 129.7 Hz); 9.4 (qt, $CH_2\underline{C}H_3$, $^1J_{CH}$ = 126.8 Hz); 32.1 (tq, $\underline{C}H_2CH_3$, $^1J_{CH}$ = 128.5 Hz); 41.9 (dm, $H_d\underline{C}$-CH_c, $^1J_{CH}$ = 136.4 Hz); 42.8 (qq, $NN(Me)_2$, $^1J_{CH}$ = 137.7 Hz, $^2J_{CH}$ = 3.7 Hz); 49.8 (dm, H-$\underline{C}$-CH_3, $^1J_{CH}$ = 120.7 Hz); 51.7 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 146.1 Hz); 52 (q, $CO_2\underline{C}H_3$, $^1J_{CH}$ = 150.3 Hz); 53.2 (dm, H_dC-$\underline{C}H_c$, $^1J_{CH}$ = 135.8 Hz); 60.3 (dm, $H_e\underline{C}$-C=O, $^1J_{CH}$ = 129.7Hz); 78.3 (m, OH-$\underline{C}$-C_2H_5); 132.7 (dm, H-$\underline{C}$=NN$(Me)_2$, $^1J_{CH}$ = 163.2 Hz); 169.7 (m, $\underline{C}O_2CH_3$); 174.7 (m, $\underline{C}O_2CH_3$); 203.9 (m, H_3CO_2C-C-$\underline{C}$=O).

X-Ray Crystallographic Analysis Data for 4bc : $C_{16}H_{26}O_6N_2$.

Crystal data for $C_{16}H_{26}O_6N_2$ (**4bc**), Mr = 342.40, orthorhombic, $p2_12_12_1$, a = 5.675(7), b = 17.185(5), c = 18.397(7)Å, V = 1794(2)$Å^{-3}$, Z = 4, D_x = 1.268 $Mg.m^{-3}$, λ(MoKα) = 0.70926Å, μ = 0.906 cm^{-1}, F(000) = 736, T = 293 K, final R = 0.035 for 1495 observations. The sample (0.40*0.45*0.45 mm) is studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$ = 50°, scan $\omega/2\theta$ = 1, t_{max} = 60 s, range HKL : H 0,6 K 0,20 L 0,21, intensity controls without appreciable decay (0.4%) gives 1877 reflections from which 1495 independant with $I>1.5\sigma(I)$. After Lorenz and polarization corrections the structure was solved with Direct Method which reveals all the non-hydrogen atoms of the structure. After isotropic (R = 0.11), then anisotropic refinement (R = 0.075), all the hydrogen atoms are found with a Fourier Difference between 0.46 and 0.18 $e.Å^{-3}$. The whole structure was refined by the full-matrix least-square techniques (use of F magnitude ; x, y, z, β_{ij} for N, O and C atoms and x, y, z for H atoms ; 296 variables and 1495 observations ; $w = 1/\sigma(F_o)^2=[\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R = 0.037, R_w = 0.035 and S_w = 0.677 (residual $\Delta\rho \leq 0.15$ e $Å^{-3}$). Atomic scattering factors from International Tables for X-ray Crystallography (1974)[20]. All the calculations were performed on a Digital MicroVAX3100 computer with the MOLEN package[21]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

5-hydroxyisopropyl-2,4-diethoxycarbonyl-3-(dimethylhydrazonomethyl)-6-dimethyl-cyclohexan-1-one (4bd)

High-resolution MS (m/z) : Calcd M^+ 398.2416. Found 398.2417.

Ethyl-2-acetyl-4-dimethylhydrazonobut-2-enoate (6bb)

This compound was obtained from the mixture of **1b** (0.5g, 5 mmol), ethyl acetoacetate **2b** (1.30g, 10 mmol) and piperidine (0.01 mL ; 0.009g ; 0.02 eq.) after standing 6 days at room temperature. Two isomers (53/47) were isolated as yellow oil from chromatography on silica gel (eluent : CH_2Cl_2/ethyl acetate 23/1). (9% yield). (Found : C, 56.59 ; H, 7.48 ; N, 12.77. $C_{10}H_{16}N_2O_3$ requires C, 56.59 ; H, 7.60 ; N, 13.20). High-resolution mass spectroscopy MS (m/z) : Calcd M^+ 212.1161. Found 212.1152. ^1H NMR ($CDCl_3$) δ : 1.3 (t, 3H, $CO_2CH_2\underline{CH_3}$); 1.35 (t, 3H, $CO_2CH_2\underline{CH_3}$); 2.4 (s, 3H, $CO\underline{CH_3}$); 2.46 (s, 3H, $CO\underline{CH_3}$); 3.18 (s, 6H, $N(Me)_2$); 3.2 (s, 6H, $N(Me)_2$); 4.27 (q, 2H, $CO_2\underline{CH_2}CH_3$); 4.3 (q, 2H, $CO_2\underline{CH_2}CH_3$); 7.3-7.7 (m, 4H, 2 H-C=C and 2 H-C=N). ^{13}C NMR ($CDCl_3$) δ : 14.3 (2qt, $2CO_2CH_2\underline{C}H_3$, $^1J_{CH}$ = 127 Hz); 28.2 (q, $CO\underline{C}H_3$, $^1J_{CH}$ = 128 Hz); 31.4 (q, $CO\underline{C}H_3$, $^1J_{CH}$ = 127 Hz); 42.8 (qq, $N(\underline{C}H_3)_2$, $^1J_{CH}$ = 138 Hz); 42.9 (qq, $N(\underline{C}H_3)_2$, $^1J_{CH}$ = 138 Hz); 60.5 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 148 Hz); 60.7 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 148 Hz); 123.6 (s, $H_3CCO\text{-}\underline{C}\text{-}CO_2CH_2CH_3$); 126.3 (d, H-$\underline{C}$=N, $^1J_{CH}$ = 166 Hz); 126.3 (s, $H_3CCO\text{-}\underline{C}\text{-}CO_2CH_2CH_3$); 127.2 (d, H-$\underline{C}$=N, $^1J_{CH}$ = 166 Hz); 145.8 (dd, H-$\underline{C}$=C, $^1J_{CH}$ = 157 Hz, $^2J_{CH}$ = 7 Hz); 147.6 (dd, H-$\underline{C}$=C, $^1J_{CH}$ = 157 Hz, $^2J_{CH}$ = 7 Hz); 166.7 (m, $\underline{C}O_2CH_2CH_3$); 166.8 (m, $\underline{C}O_2CH_2CH_3$); 195.9 (m, $CH_3\underline{C}O$); 199.8 (m, $CH_3\underline{C}O$).

Ethyl-2-isobutyryl-4-dimethylhydrazonobut-2-enoate (6bd)

This compound was obtained from the mixture of **1b** (0.5g, 5 mmol), ethyl isobutyrylacetate **2d** (1.58g, 10 mmol) and piperidine (0.15 mL ; 0.13g ; 0.3 eq.) after standing 18 hours at room temperature. Two isomers (55/45) are isolated as yellow oil from chromatography on silica gel (eluent : CH_2Cl_2/ethyl acetate 25/1). (75% yield). (Found : C, 60.22 ; H, 8.23 ; N, 10.80. $C_{12}H_{20}N_2O_3$ requires C, 59.98 ; H, 8.39 ; N, 11.66). High-resolution mass spectroscopy MS (m/z) : Calcd M^+ 240.1473. Found 240.1471. ^1H NMR ($CDCl_3$) δ : 1.10 (broad d, 6H, $CH(\underline{CH_3})_2$); 1.12 (broad d, 6H, $CH(\underline{CH_3})_2$); 1.32 (td, 3H, $CO_2CH_2\underline{CH_3}$); 1.35 (td, 3H, $CO_2CH_2\underline{CH_3}$); 3.15 (s, 6H, $N(Me)_2$); 3.17 (s, 6H, $N(Me)_2$); 3.27 (sext.d, 2H, $C\underline{H}(CH_3)_2$); 4.25 (qt, 2H, $CO_2\underline{CH_2}CH_3$); 4.31 (qt, 2H, $CO_2\underline{CH_2}CH_3$); 7.26 (d, 1H, $H_aC\text{-}C\underline{H}_b$, $^3J_{AB}$ = 9.82 Hz); 7.33 (d, 1H, H_aC-

$C\underline{H}_b$, $^3J_{AB}$ = 9.84 Hz); 7.41 (d, 1H, $\underline{H}_aC$-CH_b, $^3J_{AB}$ = 9.73 Hz); 7.53 (d, 1H, $\underline{H}_aC$-CH_b, $^3J_{AB}$ = 9.86 Hz). ^{13}C NMR ($CDCl_3$) δ : 14.3 (qm, 2 $CO_2CH_2\underline{C}H_3$, $^1J_{CH}$ = 127 Hz); 18.5 (qquint., $CH(\underline{C}H_3)_2$, $^1J_{CH}$ = 127.4 Hz, $^2J_{CH}$ = 5 Hz); 19.1 (qquint., $CH(\underline{C}H_3)_2$, $^1J_{CH}$ = 127.6 Hz, $^2J_{CH}$ = 4.8 Hz); 36.9 (dquint., $\underline{C}H(CH_3)_2$, $^1J_{CH}$ = 129 Hz, $^2J_{CH}$ = 4 Hz); 39.6 (dquint., $\underline{C}H(CH_3)_2$, $^1J_{CH}$ = 131 Hz, $^2J_{CH}$ = 4 Hz); 42.8 (qm, 2 $NN(\underline{C}H_3)_2$, $^1J_{CH}$ = 138 Hz); 60.6 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 147.5 Hz); 60.7 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 147.5 Hz); 60.7 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 147.5 Hz); 125.2 (s, $(Me)_2CHCO\text{-}\underline{C}\text{-}CO_2CH_2CH_3$); 126.2 (s, $(Me)_2CHCO\text{-}\underline{C}\text{-}CO_2CH_2CH_3$); 126.4 (broad d, 2 H-$\underline{C}$=N, $^1J_{CH}$ = 165.6 Hz); 144.4 (dd, H-$\underline{C}$=C, $^1J_{CH}$ = 156.5 Hz, $^2J_{CH}$ = 8 Hz); 145.7 (dd, H-$\underline{C}$=C, $^1J_{CH}$ = 154 Hz, $^2J_{CH}$ = 11 Hz); 166.4 (m, $\underline{C}O_2CH_2CH_3$); 166.9 (m, $\underline{C}O_2CH_2CH_3$); 203.3 (m, $\underline{C}OCH(CH_3)_2$); 207.3 (m, $\underline{C}OCH(CH_3)_2$).

Ethyl-2-benzoyl-4-dimethylhydrazonobut-2-enoate (6be)

This compound was prepared by simple mixing of the hydrazone **1b** (0.5g, 5 mmol) with ethyl benzoylacetate **2e** (0.96g, 5 mmol) and piperidine (0.15 mL ; 0.13g ; 0.3 eq.). After standing 18 hours at room temperature, a mixture of Z,E isomers (67/33) (unseparable and not assigned) is obtained as yellow oil from chromatography on silica gel (eluent : diethyl ether/petroleum ether 1/1). (70% yield). (Found : C, 64.44 ; H, 6.62 ; N, 10.16. $C_{15}H_{18}N_2O_3$ requires C, 65.67 ; H, 6.61 ; N, 10.21). High-resolution mass spectroscopy MS (m/z) : Calcd M^+ 274.1317. Found 274.1318. ^1H NMR ($CDCl_3$) δ : 1.06 (t, 3H, $CO_2CH_2\underline{C}H_3$, J = 7 Hz); 1.1 (t, 3H, $CO_2CH_2\underline{C}H_3$, J = 7 Hz); 3.03 (s, 6H, $N(Me)_2$); 3.18 (s, 6H, $N(Me)_2$); 4.1 (q, 2H, $CO_2\underline{C}H_2CH_3$, J = 7 Hz); 4.14 (q, 2H, $CO_2\underline{C}H_2CH_3$, J = 7 Hz); 6.9 (d, 1H, $\underline{H}$-C=C, J = 9.9 Hz); 7.41 (d, 1H, $\underline{H}$-C=C, J = 9.9 Hz); 7.44-7.9 (m, 12H, 2 C_6H_5 and 2 H-C=N). ^{13}C NMR ($CDCl_3$) δ : 13.8 (qt, $CO_2CH_2\underline{C}H_3$, $^1J_{CH}$ = 127 Hz, $^2J_{CH}$ = 2.5 Hz); 14 (qt, $CO_2CH_2\underline{C}H_3$, $^1J_{CH}$ = 127 Hz, $^2J_{CH}$ = 2.7 Hz); 42.6 (qq, $N(\underline{C}H_3)_2$, $^1J_{CH}$ = 135.4 Hz); 42.8 (qq, $N(\underline{C}H_3)_2$, $^1J_{CH}$ = 135.3 Hz); 60.45 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 143.9 Hz, $^2J_{CH}$ = 4.3 Hz); 60.65 (tq, $CO_2\underline{C}H_2CH_3$, $^1J_{CH}$ = 147.6 Hz, $^2J_{CH}$ = 4.7 Hz); 124.9 (s, $PhOC\text{-}\underline{C}\text{-}CO_2CH_2CH_3$); 125.3 (dd, H-$\underline{C}$=N, $^1J_{CH}$ = 165.6 Hz); 125.6 (s, $PhOC\text{-}\underline{C}\text{-}CO_2CH_2CH_3$); 126.8 (dd, H-$\underline{C}$=N, $^1J_{CH}$ = 166.7 Hz); 128.2 (ddd, o-C de C_6H_5); 128.5 (ddd, o-C de C_6H_5); 128.8 (dm, m-C de C_6H_5); 128.9 (dm, m-C de C_6H_5); 132 (dtt, p-C de C_6H_5); 133 (dtt, p-C de C_6H_5); 138.1 (td, C IV de C_6H_5); 138.8 (td, C IV of C_6H_5); 144.3 (dd, H-$\underline{C}$=C, $^1J_{CH}$ = 158.8 Hz, $^2J_{CH}$ = 8.8 Hz); 147.4 (dd, H-$\underline{C}$=C, $^1J_{CH}$ = 155 Hz, $^2J_{CH}$ = 8.9 Hz); 165.9 (m, $\underline{C}O_2CH_2CH_3$); 166.4 (m, $\underline{C}O_2CH_2CH_3$); 194.3 (m, $C_6H_5\text{-}\underline{C}O$); 195 (m, $C_6H_5\text{-}\underline{C}O$).

2-phenyl-4-benzoylpyridazin-3(2H)-one (5e)

5e is obtained by simple mixing of **1a** (0.74g, 5 mmol) with **2e** (0.96g, 5 mmol) and piperidine (0.15 mL ; 0.13g ; 0.3 eq.) after standing 15 minutes at room temperature. Pure **5e** is isolated after chromatography on alumina (eluent : CH_2Cl_2/petroleum ether 8/2). (72% yield ; m.p 173°C). (Found : C, 73.38 ; H, 4.27 ; N, 9.98. $C_{17}H_{12}N_2O_2$ requires C, 73.94 ; H, 4.38 ; N, 10.14). High resolution mass spectroscopy (m/z) : Calcd M^+ 276.0898. Found 276.0928. ^1H NMR ($CDCl_3$) δ : 7.36 (d,1H, $\underline{H}_bC$-CH_a, $^3J_{AB}$ = 3.9 Hz); 7.39-7.89 (m, 10H, 2 C_6H_5); 8.01 (d, 1H, H_bC-$C\underline{H}_a$, $^3J_{AB}$ = 3.9 Hz). ^{13}C NMR ($CDCl_3$) δ : 125.3-129.6/134.3 (m, C_6H_5); 130.3 (dd, $H_b\underline{C}$-CH_a, $^1J_{CH}$ = 167.5 Hz, $^2J_{CH}$ = 8.4 Hz); 136.4 (dd, H_bC-$\underline{C}H_a$, $^1J_{CH}$ = 189.8 Hz, $^2J_{CH}$ = 2.9 Hz); 157.7 (d, N-$\underline{C}$O); 192.2 (q, $C_6H_5\text{-}\underline{C}O$).

Typical procedure for microwave reaction :

2-phenyl-4-isobutyrylpyridazin-3(2H)-one (5d)

A mixture of hydrazone **1a** (0.74g, 5 mmol), ethyl isobutyrylacetate (0.79g, 5 mmol) and piperidine (0.15 mL, 0.13g, 0.3 eq) was placed in a pyrex tube and introduced into a Maxidigest MX350 Prolabo microwave reactor (2.45 GHz) fitted with a rotational system and adjustable power with in range 0-300W and a wave guide (monomode T_{01}). Microwave irradiation was carried with a temperature monitored at 90°C during 20 minutes

(power 30W). The mixture was cooled to room temperature, the crude residue was characterized by ^1H NMR and purified by chromatography on alumina column (eluent : CH_2Cl_2/Ethyl acetate 1/1 then CH_2Cl_2/petroleum ether 5/4). (53% yield; m.p 67°C). (Found : C, 69.34 ; H, 5.96 ; N, 11.61. $C_{14}H_{14}N_2O_2$ requires C, 69.41 ; H, 5.82 ; N, 11.56). High resolution mass spectroscopy (m/z) : Calcd M^+ 242.1055. Found 242.1053. ^1H NMR ($CDCl_3$) δ : 1.17 (d, 6H, $CH(\underline{CH_3})_2$); 3.80 (heptuplet, 1H, $\underline{CH}(CH_3)_2$); 7.41-7.60 (m, 5H, C_6H_5); 7.65 (d,1H, $\underline{H_b}C\text{-}CH_a$, $^3J_{AB}$ = 4 Hz); 8 (d, 1H, $H_bC\text{-}\underline{CH_a}$, $^3J_{AB}$ = 4 Hz). ^{13}C NMR ($CDCl_3$) δ : 17.9 (q quint., $CH(\underline{C}H_3)_2$, $^1J_{CH}$ = 127.8 Hz, $^2J_{CH}$ = $^3J_{CH}$ = 5 Hz); 39.3 (d hept., $\underline{C}H(CH_3)_2$, $^1J_{CH}$ = 131.8 Hz, $^2J_{CH}$ = 4.1 Hz); 125.4-128.8 (m, C_6H_5); 131.8 (dd, $H_b\underline{C}\text{-}CH_a$, $^1J_{CH}$ = 167.8 Hz, $^2J_{CH}$ = 8.5 Hz); 136.5 (dd, $H_bC\text{-}\underline{C}H_a$, $^1J_{CH}$ = 189.3 Hz, $^2J_{CH}$ = 3.4 Hz); 137.4 (dd, $\underline{C}\text{-}COCH(CH_3)_2$, $^2J_{CH}$ = 6.1 Hz, $^3J_{CH}$ = 1.8 Hz); 141.2 (m, C IV of C_6H_5); 158.3 (d, N-$\underline{C}$O); 203.8 (m, $\underline{C}OCH(CH_3)_2$).

REFERENCES AND NOTES

1. Coudert P.; Rubat C.; Couquelet J.; Fialip J.; Bastide P.; *Eur. J. Med. Chem.*; **1989**, 24, 551-555.
2. Rubat C.; Coudert P.; Tronche P.; Bastide J.; Bastide P.; Privat A.M.; *Chem. Pharm. Bull.*; **1989**, 37, 2832-2835.
3. Okushima H.; Narimatsu A.; Kobayashi M.; Furuya R.; Tsuda K.; Kitada Y.; *J. Med. Chem.*; **1987**, 30, 1157-1161.
4. Kamiya S.; Anzai M.; Nakashima T.; Sueyoshi S.; Tanno M.; *Chem. Pharm. Bull.*; **1977**, 25, 504.
5. Klein, B.; Texier-Boullet, F.; Hamelin, J.; *Synthesis* ; **1986**, 409-410.
6. Latouche, R.; Texier-Boullet, F.; Hamelin, J.; *Tetrahedron Lett.* ; **1991**, 32, 1179-82.
7. Pilard, J.F.; Klein, B.; Texier-Boullet, F.; Hamelin, J.; *Synlett* ; **1992**, 219-220.
8. Lerestif, J.M.; Bazureau, J.P.; Hamelin, J.; *Tetrahedron Lett.* ; **1993**, 34, 4639-42.
9. Rechsteiner, B.; Texier-Boullet, F.; Hamelin, J.; *Tetrahedron Let.* ; **1993**, 34, 5071-74.
10. Abdallah-El Ayoubi, S.; Texier-Boullet, F.; Hamelin, J.; *Synthesis* ; **1994**, 258-60.
11. Ruault, P.; Pilard, J.F.; Touaux, B.; Texier-Boullet, F.; Hamelin, J.; *Synlett* ; **1994**, 935-936.
12. Abdallah-El Ayoubi, S.; Texier-Boullet, F.; *J. Chem. Research(S)* ; **1995**, 208.
13. Lerestif, J.M.; Perrocheau, J.; Tonnard, F.; Bazureau, J.P.; Hamelin, J.; *Tetrahedron* ; **1995**, 6757.
14. a - Hamelin J.; Loupy A.; Mathé D.; Microwave and High Frequency Heating 1995, S^t John's college, Cambridge UK, 17-21 September **1995**. b - Jacquault P.; Texier-Boullet F.; Bazureau J.P.; Hamelin J.; PACIFICHEM 95, Honolulu, 17-22 December **1995**.
15. Jolivet S.; Texier-Boullet F.; Jacquault P.; Hamelin J.; *Heteroatom Chemistry* ; **1995**, 6, 469.
16. Commarmot R.; Didenot R.; Gardais J.F.; Rhône-Poulenc/Prolabo Patent number 84/03496. October 27th 1986. Apparatus commercialized by Prolabo under the name Synthewave 402.
17. Ste Prolabo, 54 rue Roger Salengro, 94126 Fontenay-sous-Bois, France.
18. Begtrup M.; Nytoft H.P.; *J.Chem.Soc. Perkin Trans I* ; **1985**, 81.
19. Severin Th.; Poehlman H.; *Chem. Ber.* ; **1977**, 491.
20. International Tables for X-Ray Crystallography Part. IV ed. Kynoch Press, Birmingham, **1974**. (Present distributor, D. Reidel, Dordrecht).
21. Fair C.K., Mol EN.; An Interactive Intelligent System for Crystal Structure Analysis. Ed. Enraf-Nonius, Delft, The Netherlands; **1990**.

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