SYNTHESIS OF CONFORMATIONNALY RESTRAINED ANALOGS OF 7-n-BUTYRYL-2,3-DIHYDRO-3-OXO[1,4]BENZOXAZINE, A NORMOLIPEMIC PHARMACOPHORIC PATTERN

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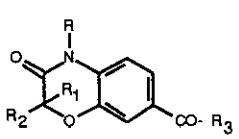
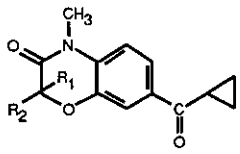
Abstract - Original conformationnaly restrained analogs of 7-n-butyryl-2,3-dihydro-3-oxo[1,4]benzoxazine , a normolipemic pharmacophoric pattern were synthesized from benzoxazinyl or benzoxazolinyl precursors.

2,3-Dihydro-2,2,4-trisubstituted 3-oxo[1,4]benzoxazines (Structure **A**, Scheme 1) are of interest in view of their structural analogy with the well known fibrates normolipemic drugs.[1] In an attempt to find new such therapeutic agents, we have reported[1] that the 7-substituted benzoxazinyl derivatives are more active than the 6-substituted isomers. Moreover, in contrast to the structure activity relationships of fibrates, we have shown[1] that the 7-acylbenzoxazine system and particularly the 7-n-butyryl one could be considered as a new normolipemic pharmacophore. We undertook therefore chemical modifications of this structure in order to increase the biological activity.[2,3] Recently one of the purpose of our investigations was to study the 7-n-butyryl chain and from this point of view we thought that rigid or semi-rigid analogs of this group deserve attention because they might favor some conformations which would be optimal for normolipemic activity. So our interest has been directed towards the synthesis of structures **B** and **C** in which the 7-n-butyryl chain is incorporated in a cyclopropylcarbonyl moiety or in an oxo cyclopentane ring (Scheme 1).

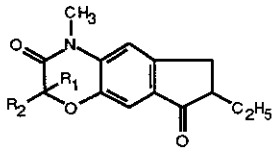
Scheme 1



[A]



[B]



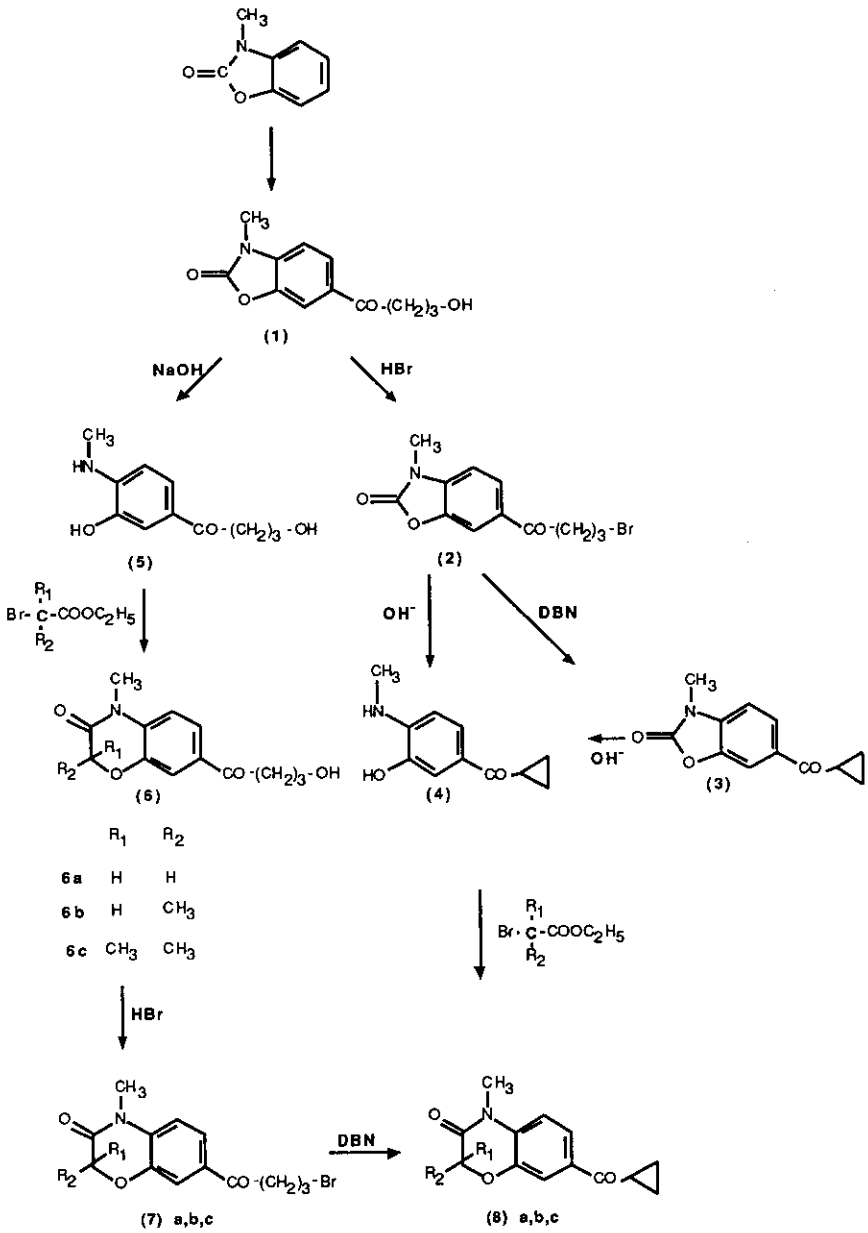
[C]

We have investigated several methods to provide access to a broad range of derivatives of structure **B** or **C** and these methods can be classified into two groups. The first one use a benzoxazinyl precursor and the second one a benzoxazolinyl starting material.

7-Cyclopropylcarbonyl-2,4-disubstituted 2,3-dihydro-3-oxo[1,4]benzoxazines (Structure B)

The first method (Scheme 2) involved reaction of 3-methyl-2-oxo-2,3-dihydro[1,3]benzoxazole with 4-chlorobutyric acid or γ-butyrolactone in polyphosphoric acid.[4] The γ-hydroxy ketone[5] (**1**) led to the o-aminophenol (**5**) by hydrolysis on heating with aqueous sodium hydroxyde.[6,7] Heterocyclisation of **5** with an ethyl α-bromocarboxylate[8] gave the 7-(4-hydroxybutyryl)benzoxazinyl compounds (**6**) which were then treated with gazeous HBr. Subsequent cyclodehydrohalogenation of the resulting 4-bromobutyryl derivatives (**7**) using 1,5-diazabicyclo[3.4.0]non-5-ene (DBN)[9] in dimethyl sulfoxide (DMSO) at room temperature gave the tittle compounds (**8**) with an overall yield of 35 % from the 2-oxo-2,3-dihydro[1,3]benzoxazole precursor. Compounds (**8**) were also obtained according to the following reaction scheme. Preliminary reaction of **1** with HBr led to the 4-bromobutyryl derivative[5](**2**). Simultaneous alkaline hydrolysis and cyclodehydrohalogenation[10] gave the 5-cyclopropylcarbonyl-2-methylaminophenol (**4**), heterocyclisation of which gave the compounds (**8**) with an equivalent overall yiel of 40 % (4 steps). Treatment of the bromobutyryl compound (**2**) with DBN led to **3** (70 % yield) which afforded **4** (60 % yield) by heating with NaOH.

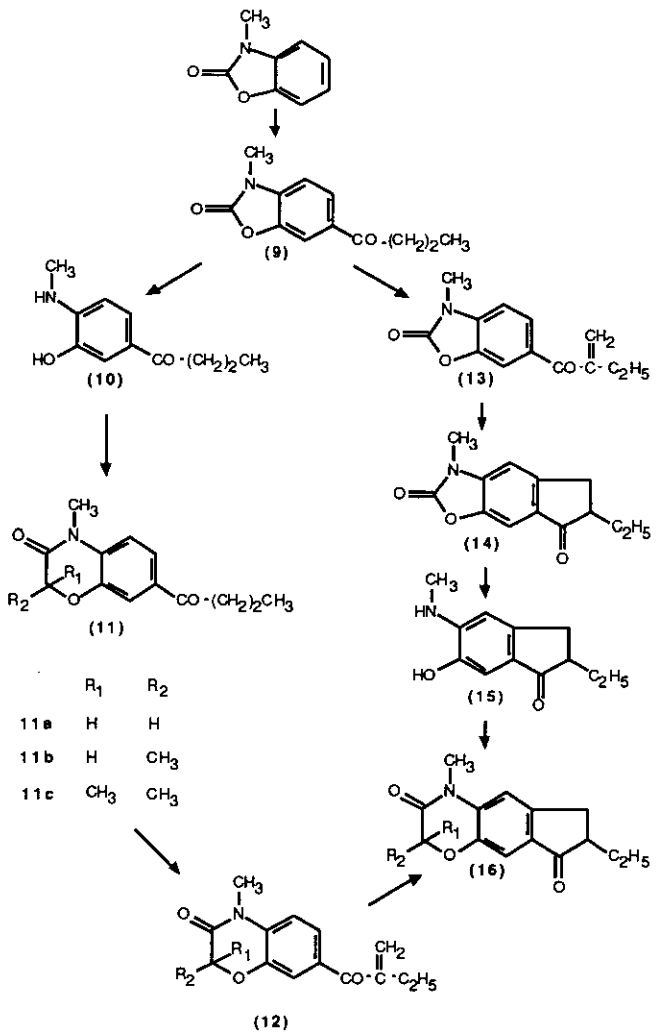
Scheme 2


(1)
NaOH
HBr
(5)
(2)
OH⁻
DBN
(6)
(4)
(3)
6a H H
6b H CH3
6c CH3 CH3
HBr
DBN
(7) a,b,c
(8) a,b,c

3,8-Dioxo-4-methyl-7-ethylcyclopenta[g]-2,3-dihydro[1,4]benzoxazines (Structure C)

Two synthetic pathways (Scheme 3) were also undertaken, one of them using intermediates which we have earlier synthesized.[1,3] In this first method (32 % overall yield ; 5 steps), acylation[1] of 3-methyl-2-oxo-2,3-dihydro[1,3]benzoxazole with butyric acid in polyphosphoric acid gave **9** which was readily hydrolysed to afford the aminophenol (**10**). Heterocyclisation of **10** with an ethyl α-bromocarboxylate and then treatment of the resulting **11** with N,N,N',N'-tetramethyldiaminomethane at 90°C in acetic anhydride [11] gave the α, β-ethylenic ketones (**12**). Heating **12** at 40°C with concentrated sulfuric acid [12] resulted in an intramolecular cyclialkylation of the aromatic ring producing the desired tricyclic analogs (**16**). On the other hand, when **9** was treated with 1,3,5-trioxane, morpholine hydrochloride and sodium acetate in acetic acid medium, involving an intermediate formation of a Mannich base followed by an elimination of amine,[13] the α, β-ethylenic ketone (**13**) was readily obtained. Cyclisation in concentrated sulfuric acid led to **14**, which was hydrolysed to **15** by heating with NaOH.The tittle compounds (**16**) were finally obtained by heterocyclisation of **15** with an overall yield of 44%(5 steps).

Scheme 3



EXPERIMENTAL

Melting points were determined on a Buchi 510 apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer 297 spectrophotometer and ^{1}H nmr spectra on a Brücker 80 MHz apparatus with TMS as internal standard. Elemental analysis were performed by the CNRS Center, Vernaison, France. Starting materials and intermediates (**1**), (**2**), (**9**), (**10**), (**11**), (**12**) were prepared by published procedures.[1,3,5]

6-Cyclopropylcarbonyl-3-methyl-2,3-dihydro-2-oxo[1,3]benzoxazole(3)

To a solution of the bromoketone (**2**) (11.3 g, 0.05 mol) in dimethyl sulfoxide (50 ml) was added dropwise (19 g, 0.15 mol) of DBN.The reaction medium was stirred at room temperature for 2h then, quenched with ice water (200 ml) and filtered under vaccuum. The solid obtained was washed with water and purified by recrystallisation from ethanol/water (1/1) to afford **3** (7.6 g, 70% yield). mp 160-164°C ; ir (KBr) : 3060-2980, 1760, 1650, 1600 cm^{-1} ; ^{1}Hnmr ($CDCl_3$) δ : 7.95-8.10 (dd, J = 3 and 8.5 Hz, 1H) ; 7.90 (d, J = 3 Hz,1H) ; 7.00 (d, J = 8.5 Hz, 1H) ; 3.45 (s, 1H) ; 2.50-2.80 (m, 1H) ; 1.00- 1.40 (m, 4H). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35 ; H, 5.06 ; N,6.45. Found : C, 66.11 ; H, 5.04 ; N, 6.46.

5-Cyclopropylcarbonyl-2-methylaminophenol (4)

A mixture of 6-(4-bromobutyryl)-3-methyl-2,3-dihydro-2-oxo[1,3]benzoxazole(**2**) (22.8 g ; 0.1 mol) in 10% aqueous NaOH (300 ml, 0.75 mol) was heated at 80°C for 1 h. After filtration of the hot mixture and treatment with concentrated HCl, product (**4**) was precipitated by adjusting the pH of the filtrate to 8 with 10% aqueous sodium carbonate. The precipitate was collected by filtration, washed with water and recrystallised from ethanol/water (1/1) (11.5 g, 60% yield). mp 170°C ; ir (KBr) : 3400, 3160, 3000-2800, 1620, 1560 cm^{-1} ; ^{1}Hnmr (acetone-d_6) δ : 8.60 (s, 1H, signal dissapeared after adding D_2O) ; 7.60 (dd, J = 4 and 8 Hz, 1H) ; 7.45 (d, J = 4 Hz, 1H) ; 6.50 (d, J = 8 Hz, 1H) ; 5.40 (s, 1H, signal dissapeared after adding D_2O) ; 2.95 (d, J = 6 Hz, 3H) ; 2.75 (m, 1H) ; 0.95 (m, 4H). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.08 ; H, 6.80 ; N, 7.32 . Found : C, 69.30 ; H, 6.96 ; N, 7.37.

5-(4-Hydroxybutyryl)-2-methylaminophenol (5)

Compound (**1**) (47.05 g, 0.2 mol) in 10% aqueous sodium hydroxide (800 ml, 2 mol) was heated for 1 h at 80°C. After filtration of the hot mixture and acidification with concentrated HCl, the pH was adjusted to 8 with 10% aqueous sodium carbonate. The precipitate was collected by filtration, washed with water and recrystallised from water to afford **5** (25 g, 60 % yield). mp 126-128°C ; ir (KBr) : 3420-3260, 2940-2800, 1640, 1590 cm^{-1} ; ^{1}Hnmr (DMSO-d_6) δ: 8.50 (s, 1H, signal dissapeared after adding D_2O) ; 7.40 (dd, J = 2 and 8 Hz, 1H) ; 7.26 (d, J = 2 Hz,1H) ; 6.43 (d, J = 8 Hz, 1H) ; 5.56 (s, 1H) ; 3.20 (t, J = 7 Hz, 2H) ; 2.82 (m, 3H) ; 2.78 (s, 3H) ; 1.74 (m, 2H). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14 ; H, 7.18, N, 6.69. Found : C, 63.35 ; H, 7.12 ; N, 6.61.

General Procedure for the Synthesis of 7-(-4-Hydroxybutyryl)-2,4-disubstituted 2,3-Dihydro-3-oxo[1,4]benzoxazines (6 a-c).

To a solution of the 2-aminophenol (**5**) (10.5 g, 0.05 mol) in dimethyl sulfoxide (100 ml) were successively added sodium ethoxide (3.4 g, 0.05 mol) and then, dropwise, the appropriated ethyl α-halogenated carboxylate (0.05 mol). After stirring for 3 h, the solution was poured into ice water (200 ml) and the precipitate (**6**) was collected by filtration and recrystallised from an appropriate solvent (Table I).

Table I. Physical and spectral data of compounds (6).

Compd	yield % (Solvent)	mp (°C)	ir (KBr) ν C=O ν OH	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) calcd./found C	H	N
6a	75 (ethanol)	130	1665 3460	7.80 (dd, J = 3 and 8 Hz, 1H) ; 7.60 (d, J = 3 Hz, 1H) ; 7.10 (d, J = 8 Hz, 1H) ; 4.70 (s, 2H) ; 3.60 (t, J = 7 Hz, 2H) 3.40 (s, 3H) ; 3.10 (t, J = 7 Hz, 2H) ; 2.40 (m, 2H) ; 2.2 (s, 2H)	$C_{13}H_{15}NO_4$	62.63 62.46	6.06 5.93	5.62 5.69
6b	75 (water)	108	1665 3460	7.80 (dd, J = 2.9 and 8.8 Hz, 1H) ; 7.65 (d, J = 2.9 Hz, 1H) ; 7.00 (d, J = 8.8 Hz, 1H) ; 4.70 (q, J = 7 Hz, 1H) ; 3.75 (t, J = 6.5 Hz, 2H) : 3.40 (s, 3H) ; 3.20 (t, J = 6.5 Hz, 2H) ; 2.00 (m, 3H) ; 1.55 (d, 3H)	$C_{14}H_{17}NO_4$	63.86 63.64	6.50 6.65	5.32 5.39
6c	60 (cyclohexane)	82-84	1660 3470	7.80 (dd, J = 3 and 8.5 Hz, 1H) ; 7.60 d, J = 3 Hz, 1H) ; 7.00 (d, J = 8.5 Hz, 1H) ; 3.70 (t, J = 6 Hz, 2H) ; 3.40 (s, 3H) ; 3.10 (t, J = 6 Hz, 2H) ; 2.30 (s, 1H) ; 2.00 (m, 2H) ; 11.50 (s, 6H)	$C_{15}H_{19}NO_4$	64.96 65.08	6.90 6.72	5.05 5.07

General Procedure for the Synthesis of 7-(-4-Bromobutyryl)-2,4-disubstituted 2,3-Dihydro-3-oxo[1,4]benzoxazines (7 a-c)

A solution of **6** (0.05 mol) in anhydrous acetone (100 ml) was stirred at room temperature with gazeous HBr (0.055 mol) during 2 h. After filtration and evaporation of the filtrate the solid residue was crystallised from an appropriate solvent (Table II).

Table II. Physical and spectral data of compounds (7)

Compd	yield % (Solvent)	mp (°C)	ir (KBr) ν C=O	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) calcd./found C	H	N
7a	80 (acetone)	122-124	1660	7.80 (dd, J = 3 and 8.9 Hz, 1H) ; 7.60 (d, J = 3 Hz, 1H) ; 7.00 (d, J = 8.9 Hz, 1H) ; 4.60 (s, 2H) ; 3.55 (t, J = 7.4 Hz, 2H) ; 3.40 (s, 3H) ; 3.15 (t, J = 7.4 Hz, 2H) ; 2.35 (m, 2H)	$C_{13}H_{14}NO_3Br$	50.00 50.07	4.51 4.60	4.48 4.48
7b	75 (ethanol)	92-96	1680 1660	7.80 (dd, J = 2.7 and 8.3 Hz, 1H) ; 7.60 (d, J = 2.7 Hz, 1H) ; 7.00 (d, J = 8.3 Hz, 1H) ; 4.65 (q, J = 7 Hz,1H) ; 3.55 (t, J = 6.9 Hz, 2H) : 3.40 (s, 3H) ; 3.15 (t, J = 7 Hz,2H) ; 2.30 (m, 2H) ; 1.60 (d, J = 6.9 Hz, 3H)	$C_{14}H_{16}NO_3Br$	51.23 51.29	4.94 4.91	4.29 4.23
7c	85 (acetone)	110-112	1670 1655	7.80 (dd, J = 2.8 and 8.3 Hz, 1H) ; 7.60 d, J = 2.8 Hz, 1H) ; 7.00 (d, J = 8.3 Hz, 1H) ; 3.60 (t, J = 6.9 Hz, 2H) ; 3.40 (s, 3H) ; 3.15 (t, J = 6.9 Hz, 2H) ; 2.40 (m, 2H) ; 1.50 (s, 6H)	$C_{15}H_{18}NO_3Br$	52.93 52.67	5.33 5.11	4.11 4.16

General Procedure for the Synthesis of 7-(Cyclopropylcarbonyl)-2,4-disubstituted 2,3-Dihydro-3-oxo[1,4]benzoxazines (8 a-c)

These compounds (Table III) were prepared from **7** (0.05 mol) in dimethyl sulfoxyde (50 ml) by treatment with DBN (18,5 g, 0.15 mol) as described for the preparation of **3**.

Table III. Physical and spectral data of compounds (8)

Compd	yield % (Solvent)	mp (°C)	ir (KBr) $\nu_{C=O}$	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) calcd./found C	H	N
8 a	80 (ethanol)	110-112	1675 1655	7.80 (dd, J = 3 and 8.5 Hz, 1H) ; 7.65 (d, J = 3 Hz, 1H) ; 7.00 (d, J = 8.5 Hz, 1H) ; 4.70 (s, 2H) : 3.40 (s, 3H) 2.60 (m, 1H) ; 1.10 (m, 4H)	$C_{13}H_{13}NO_3$	66.93 66.99	6.48 6.54	6.00 6.00
8 b	70 (cyclohexane)	87	1670 1650	7.90 (dd, J = 3 and 8 Hz, 1H) ; 7.70 (d, J = 3 Hz, 1H) ; 7.00 (d, J = 8 Hz, 1H) 4.70 (q, J = 6.6 Hz,1H) ; 3.40 (s, 3H) ; 2.60 (m, 1H) ; 1.60 (d, J = 6.6 Hz, 3H) ; 1.20 (m, 4H)	$C_{14}H_{15}NO_3$	68.58 68.45	6.16 6.14	5.70 5.41
8 c	50 (n. hexane)	51-53	1670 1650	7.90 (dd, J = 3 and 8.8 Hz, 1H) : 7.70 (d, J = 3 Hz, 1H) ; 7.00 (d, J = 8.8 Hz, 1H) ; 3.40 (s, 3H) ; 2.20 (m, 1H) ; 1.50 (s, 6H) ; 1.20 (m, 4H)	$C_{15}H_{17}NO_3$	69.47 69.59	6.60 6.63	5.40 5.47

6-(2-Methylenebutyryl)-3-methyl-2,3-Dihydro-2-oxo[1,3]benzoxazole (13)

A mixture of **9** (4.38 g, 0.02 mol), 1,3,5-trioxane (2.70 g, 0.03 mol), morpholine hydrochloride (3.66 g, 0.03 mol) and sodium acetate (10 g, 0.12 mol) in acetic acid (150 ml) was heated at reflux for 5 h. After hot filtration and evaporation of the filtrate, the residue taken off with water (500 ml) was made basic with 10 % aqueous NaOH and extracted with ethyl acetate. The organic layers were evaporated and the residue was crystallised from cyclohexane (3.7 g, 80 % yield) mp 86-88°C ; ir (KBr) : 3060-2920, 1775, 1640, 1600, 930 cm^{-1} ; ^{1}Hnmr ($CDCl_3$) δ : 7.80 (dd, J = 3 and 8.8 Hz,1H) ; 7.25 (s, 1H) 7.20 (d, J = 8.8 Hz,1H) ; 5.85 (s, 1H) ; 5.55 (s, 1H) ; 3.50 (s, 3H) ; 2.50 (q, J = 7.4 Hz, 2H) ; 1.15 (t, J = 7.4 Hz, 3H). Anal. Calcd for $C_{13}H_{13}NO_3$: C,67.51 ; H, 5.67 ; N, 6.06. Found : C, 67.90 ; H, 5.84 ; N, 6.06.

General Procedure for the Synthesis of 3,8-Dioxo-4-methyl-7-ethylcyclopenta[g]-2,3-Dihydro[1,4]benzoxazines (16 a-c)

Procedure A :

A solution of the appropriate compound (**12**) (0.03 mol) in concentrated sulfuric acid (30 ml) was heated at 40°C for 4 h. The mixture was then cooled and poured into cold water. The separated solid was filtered, washed with water, dried and crystallised from an appropriate solvent (Table IV).

Table IV. Physical and spectral data of compounds (16)

Compd	yield % (Solvent)	mp (°C)	ir (KBr) ν C=O	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) calcd./found C	H	N
16a	85 (acetone)	147	1700 1670	7.35 (s, 1H) ; 7.00 (s, 1H) ; 4.60 (s, 2H) 3.45 (s, 3H) ; 2.50-2.30 (m, 3H) ; 1.75 (m, 2H) ; 1.00 (t, J = 7.7 Hz, 3H)	$C_{14}H_{15}NO_3$	68.55 68.49	6.16 6.04	5.71 5.71
16b	70 (isopropanol)	120-122	1670	7.40 (s, 1H) ; 7.00 (s, 1H) ; 4.60 (q, J = 7 Hz, 1H) ; 3.45 (s, 3H) ; 2.60-3.20 (m, 3H) ; 1.90 (m, 2H) ; 1.60 (d, J = 7 Hz, 3H) ; 1.00 (t, J = 7 Hz, 3H)	$C_{15}H_{17}NO_3$	69.47 69.59	6.60 6.51	5.40 5.24
16c	90 (methanol)	110-112	1675	7.30 (s, 1H) ; 7.00 (s, 1H) ; 3.45 (s, 3H) 3.25-2.50 (m, 3H) ; 1.90 (m, 2H) ; 1.50 (s, 6H) ; 1.00 (t, J = 7 Hz, 3H)	$C_{16}H_{19}NO_3$	70.30 70.02	7.00 6.93	5.12 5.17

Procedure B :

Step a : A solution of 6-(2-methylenebutyryl)-3-methyl-2,3-dihydro-2-oxo[1,3]benzoxazole (**13**) (7 g, 0.03 mol) in concentrated sulfuric acid (30 ml) was heated according to the same procedure described above. After typical treatment 2,7-dioxo-3-methyl-6-ethyl-cyclopenta[f]-2,3-dihydro-2-oxo[1,3]benzoxazole (**14**) was obtained and purified by recrystallisation from ethanol (6.25 g, 90% yield). mp 118-119°C ; ir (KBr) : 1810-1775, 1700-1675 cm^{-1} ; ^{1}Hnmr ($CDCl_3$) δ : 7.75 (s, 1H) ; 7.00 (s, 1H) ; 3.45 (s, 3H) ; 1.20-3.40 (m, 5H) ; 1.00 (t, J = 7 Hz,3H). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67,51 ; H, 5,67 ; N, 6.06. Found : C, 67.57 ; H, 5.48 ; N, 6.05.

Step b : Compound (**15**) was prepared from **14** in 75% yield by the same procedure used for **5** and after crystallisation from aqueous ethanol/water (9/1) (mp 192-194°C), it was cyclized to compounds (**16**) with 70-80% yield.

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Received, 24th June, 1991