Reaction of 5-Substituted-2-amino-2-oxazolines with Ethoxycarbonyl Isocyanate. A Route to 2,3,6,7-tetrahydro-4*H*-Oxazolo[3,2-*a*]-1,3,5-triazine-2,4-diones

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The reaction of 2-amino-2-oxazolines with ethoxycarbonyl isocyanate was investigated in order to access to fused 1,3,5-triazine-2,4-diones with a potential 5-HT_2 antagonist activity. The reaction leads to 2,3,6,7-tetrahydro-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-diones and to 1-carbethoxy-3-(2-iminooxazolidine)ureas. During the carbamoylation the regioselectivity seems to be related to the strong nucleophilic character of the endo nitrogen atom of 2-amino-2-oxazolines. The structures of two compounds were studied by X-ray crystallography. *N*-Substituted compounds have been prepared by alkylation of the 2,3,6,7-tetrahydro-7-phenoxymethyl-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-dione.

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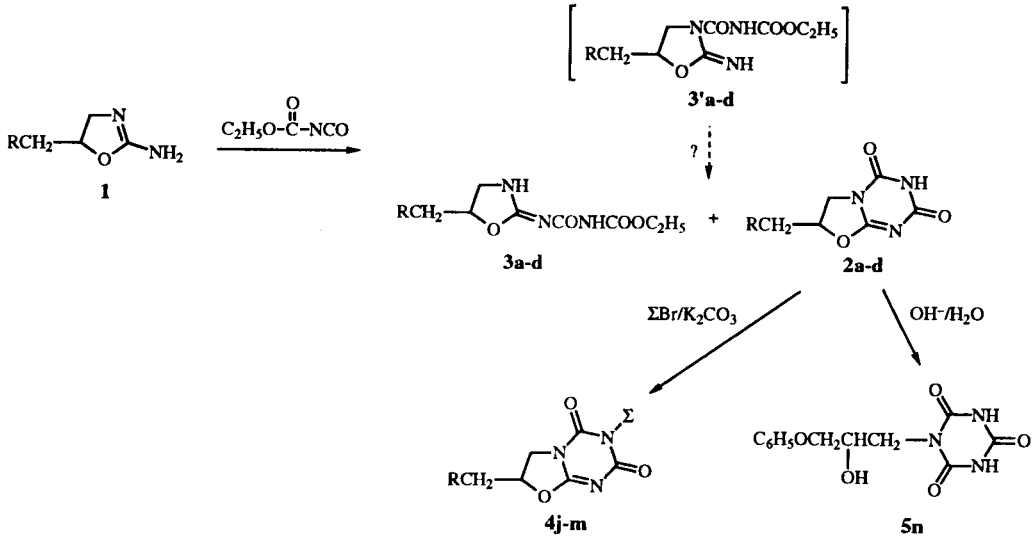
Fused 1,3,5-triazine-2,4-diones have become more interesting as potential 5-hydroxy tryptamine antagonists (5-HT_2 antagonists) related to ketanserin [1-3]. Different synthetic routes have been developed, a number of them involving a cyclocondensation from an aminoheterocyclic compound [4-6]. Ethoxycarbonyl isocyanate proved useful as a synthetic reagent suitable for cyclocondensation reactions [7,8]. For several years we have mainly focused our attention on the use of 2-amino-2-oxazolines as synthons, and we investigated their reactivity towards dielectrophilic compounds with the purpose of cyclocondensation reactions [9,10].

We now report the results of the reaction of 2-amino-2-oxazolines with ethoxycarbonyl isocyanate giving the expected fused 1,3,5-triazine-2,4-diones, and 1-carbethoxy-3-(2-iminooxazolidine)ureas. Preliminary investigation on the reactivity of the 1,3,5-triazine-2,4-diones is also presented.

Scheme 1. Reaction Pathway and List of Compounds Synthesized.



R	Σ	No.	R	Σ	No.
t-butoxy	H	2a, 3a	phenoxy	methyl	4i
phenoxy	H	2b, 3b	phenoxy	benzyl	4j
(3-methyl)phenoxy	H	2c, 3c	phenoxy	allyl	4k
(2,6-dimethyl)phenoxy	H	2d, 3d	phenoxy	phenacyl	4l
			phenoxy	2,3-epoxypropyl	4m

The addition of ethoxycarbonyl isocyanate to dichloromethane solutions of the appropriate 5-substituted 2-amino-2-oxazoline **1** at 0° gives the insoluble 2,3,6,7-tetrahydro-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-diones **2** together with soluble compounds, further identified by X-ray crystallography as the 1-carbethoxy-3-(2-iminooxazolidine)ureas **3** (Scheme 1).

It is generally assumed that ethoxycarbonyl isocyanate reacts at room temperature with most nucleophilic compounds as the isocyanate group [1,11-13]. As both nitrogen atoms of 2-amino-2-oxazolines are potent nucleophilic centers, the question of the regioselectivity during the carbamoylation must be evoked [14,15]. Studying the reaction of arylisocyanates on 2-amino-2-oxazolines we recently concluded that the endocyclic nitrogen is always the most potent nucleophilic center, and consequently the most reactive center, but we noticed the possibility of intramolecular *N/N'*-rearrangement reactions [16]. Whereas the formation of **2** may be related to the carbamoylation of ethoxycarbonyl isocyanate on the endocyclic nitrogen followed by a subsequent cyclisation with a loss of ethanol, the formation of the 1-carbethoxy-3-(2-iminooxazolidine)urea **3** cannot be simply related to the reaction of ethoxycarbonyl isocyanate on the exo *N*-atom. In any case, the formation of an unstable 2-iminooxazolidine substituted on the endo *N*-atom of **3'** (kinetically controlled product) could be the first step of the reaction. Then, besides the cyclisation, an endo-*N*/exo-*N* rearrangement could occur, leading to **3** (thermodynamically controlled product).

We observed that the product distribution between products of types **2** and **3** depends upon the experimental conditions, and we noticed that urea formation is favoured by an increase in the temperature during the addition. On the other hand, the stability of **3**, which has been further related to its particular conformation, was confirmed. Heated for 6 hours in boiling xylene, 1-carbethoxy-3-[(5-phenoxymethyl)-2-iminooxazolidine]urea **3b** was cyclized in small amounts to the corresponding 1,3,5-triazine-2,4-dione **2b**. This result indicates that **3b** cannot have been an intermediate in the formation of **2b** by reaction of ethoxycarbonyl isocyanate with **1**, which strongly supports **3'b** as an intermediate.

The structure of **2b** has been established by X-ray crystallography (Figure 1). Bond lengths and angles show no surprising features. The Csp^2-Nsp^2 bonds in the two ureas moieties [C(13)-N(12); C(13)-N(14) and C(15)-N(14); C(15)-N(16)] are slightly longer than those observed in acyclic ureas. Consequently the Csp^2-O bonds are slightly shorter as already observed in barbituric acids. The N(12)-C(11) bond equal to 1.279(4)Å has the expected value [18]. The bicyclic system is almost planar; N(14) is in the sp^2 hybridation state as evidenced by the values of the bond angle C(13)-N(14)-C(15) = 126.1(2)° and of the

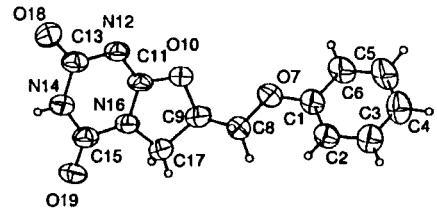


Figure 1. Molecular structure of molecule **2a** and numbering of atoms.

"nitrogen-torsion" angle H(114)-N(14)-C(15)-N(16) = -177.3(2)° referred to Andrews *et al.* [19]; [H(114) has been located in a difference Fourier map and not in a theoretical position]. The maximum deviation from planarity in the triazine ring does not exceed -7.4(5)° [N(12)-C(13)-N(14)-C(15)]. The five-membered oxazolidine ring is almost planar; C(9) does not deviate from the plane defined by O(10), C(11), N(16) and C(17) [C(9)-O(10)-C(11)-N(16) = 2.8(4)° and C(11)-N(16)-C(17)-C(9) = 0.1(3)°]. The *trans* extended bridge chain is axial relative to the bicyclic system and its orientation is defined by the torsion angle O(10)-C(9)-C(8)-O(7) = -66.8(3)°. The dihedral angle between the bicyclic system and the phenyl ring is 52.8(1)°. An hydrogen bond occurs between O(18)(x, y, z) and N(14)(1-x, y, 1/2-z) with O(18)...N(14) = 2.823(3)Å and O(18)...H(114)-N(14) = 170.5(4)°.

The 1-carbethoxy-3-(2-iminooxazolidine)urea structure **3b** has been confirmed by the presence of an NH group in the heterocycle (Figure 2). Bond lengths and angles in the molecule confirm the structure; O(13)-C(12) = 1.348(5)Å is shorter than O(13)-C(9) = 1.460(5)Å and N(11)-C(12) = 1.320(5)Å is shorter than N(11)-C(10) = 1.473(5)Å. The exocyclic C-N bond C(12)-N(14) = 1.298(5)Å, is longer than usual Csp^2=N bonds (1.279Å) (18). We then conclude to a delocalization of the double bond between atoms N(11), C(12), O(13) and N(14) with a predominance on the exocyclic bond as already observed in exo *N*-substituted compounds [20].

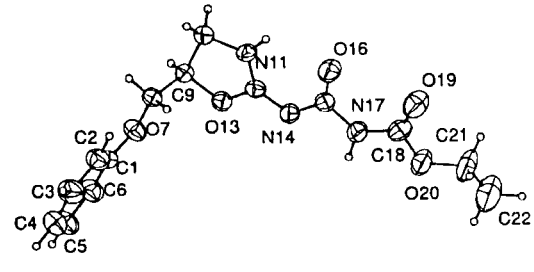


Figure 2. Molecular structure of molecule **3a** and numbering of atoms.

As in **2b** the oxazolidine ring is almost planar. The *N*-substituted side chain including the urea moiety belongs to the same plane. The torsion angles O(13)-C(12)-N(14)-C(15), C(12)-N(14)-C(15)N(17), N(14)-C(15)-N(17)-C(18) and

Table 1

Crystal Data for Compounds **2b** and **3b**

	2b	**3b**
Formula:	$C_{12}H_{11}N_3O_4$	$C_{14}H_{17}N_3O_5$
Molecular weight	261.24	307.30
Crystal size (mm)	0.22 x 0.17 x 0.13	0.3 x 0.02 x 0.15
Lattice	monoclinic	monoclinic
Sp.Gr.	C2/c	$P2_1/c$
a (Å)	24.963(3)	14.892(1)
b (Å)	7.423(1)	5.266(1)
c (Å)	15.109(2)	19.2721(2)
b (°)	122.67(2)	99.37(1)
D(g.cm^{-3})	1.47	1.37
F(000)	1088	648
Z	8	4
Temperature	293K	293K
μ(mm^{-1})	0.910	0.898
h, k, l	0 30, 0 9, -18 +18	0 17, 0 6, -22 +22
l (Å)	1.5418	1.5418
No. of reflections	2365	1766
No. of observed reflections	1486	1195
Volume (Å^3)	2356.7(1)	1491.2(3)
No. of variables	216	267
R (F)	0.044	0.043
Rw (F)	0.041	0.069

C(15)-N(17)-C(18)-O(20) are 177.1, -177.2, 173.0 and -172.1° respectively. The larger deviation from planarity is found in the terminal part of the chain: C(18)-O(20)-C(21)-C(22) = -164.2(5)°. As a consequence of the planarity, the electron delocalization observed in the five-membered ring can be extended along the chain up to the ester oxygen atom O(20). Both carbonyl groups are on the same side as the endo nitrogen of the oxazolidine ring. There is an intramolecular hydrogen bond between N(11) and O(16) with N(11)....O(16) = 2.733(4) Å and N(11)-H(111)...O(16) = 113(3)°, giving a pseudo six-membered ring H(111)-N(11)-C(12)-N(14)-C(15)-O(16).

The phenoxymethyl moiety is pseudo axial *versus* the oxazolidine ring: O(13)-C(9)-C(8)-O(7) = -63.4(3)° and *trans* extended: C(10)-C(9)-C(8)-O(7) = 177.1(3)°, C(9)-C(8)-O(7)-C(1) = 172.8(3)°. The planar conformation and the electron delocalization confer an important stability to the molecule.

Methylation of **2b** with *N,N*-dimethylformamide dimethylacetal proceeded selectively at N-3 to give the

Table 2

Bond Lengths (Å) and Angles (°) for Compound **2b**

C(1)-C(2)	1.376(5)	C(8)-C(9)	1.492(4)	C(17)-C(9)	1.533(4)
C(1)-C(6)	1.399(4)	C(9)-O(10)	1.488(4)	C(11)-N(12)	1.279(4)
C(2)-C(3)	1.386 (4)	O(7)-C(8)	1.437(3)	C(13)-N(12)	1.371(2)
C(3)-C(4)	1.377(5)	O(10)-C(11)	1.325(2)	C(13)-N(14)	1.391(4)
C(4)-C(5)	1.364(6)	C(11)-N(16)	1.361(4)	C(15)-N(14)	1.364(4)
C(5)-C(6)	1.375(4)	N(16)-C(17)	1.456(4)	C(15)-N(16)	1.382(2)
C(1)-O(7)	1.372(3)	C(13)-O(18)	1.220(4)	C(15)-O(19)	1.204(4)
C(1)-C(2)-C(3)	119.5 (3)	O(10)-C(9)-C(3)	108.0(3)	C(15)-N(16)-C(17)	126.1(3)
C(1)-C(6)-C(5)	118.4(3)	O(10)-C(9)-C(17)	104.8(2)	N(12)-C(11)-N(16)	127.3(2)
C(2)-C(3)-C(4)	120.3 (4)	C(9)-O(10)-C(11)	110.2(2)	N(12)-C(13)-N(14)	118.2(3)
C(2)-C(1)-C(6)	120.5 (2)	O(10)-C(11)-N(12)	122.3(3)	N(14)-C15)-N(16)	111.6(3)
C(2)-C(1)-O(7)	124.9(2)	O(10)-C(11)-N(16)	110.4(2)	O(18)-C(13)-N(12)	122.7(3)
C(3)-C(4)-C(5)	119.7(3)	C(8)-C(9)-C(17)	113.6(3)	O(18)-C(13)-N(14)	119.1(2)
C(4)-C(5)-C(6)	121.6(3)	C(11)-N(16)-C(15)	120.9(2)	O(19)-C(15)-N(14)	125.4(2)
C(6)-C(1)-O(7)	114.6(3)	C(11)-N(12)-C(13)	115.6(3)	O(19)-C(15)-N(16)	123.0(3)
C(1)-O(7)-C(8)	116.7(3)	C(13)-N(14)-C(15)	126.1(2)	O(7)-C(8)-C(9)	105.3(3)
		C(11)-N(16)-C(17)	112.9(2)	N(16)-C(17)-C(9)	101.6(3)

Table 3

Bond Lengths (Å) and Angles (°) for Compound **3b**

C(1)-C(2)	1.383(6)	C(8)-C(9)	1.502(5)	C(15)-O(16)	1.223(5)
C(1)-C(6)	1.344 (6)	C(9)-C(10)	1.542(6)	C(15)-N(17)	1.390(5)
C(2)-C(3)	1.395 (7)	C(10)-N(11)	1.473(5)	N(17)-C(18)	1.364(6)
C(3)-C(4)	1.375(8)	N(11)-C(12)	1.320(5)	C(18)-O(19)	1.193(6)
C(4)-C(5)	1.398(8)	C(12)-O(13)	1.348(5)	C(18)-O(20)	1.326(5)
C(5)-C(6)	1.382(7)	O(13)-C(9)	1.460(5)	O(20)-C(21)	1.449(7)
C(1)-O(7)	1.374(5)	C(12)-N(14)	1.298(5)	C(21)-C(22)	1.432(9)
O(7)-C(8)	1.432(5)	N(14)-C(15)	1.357(5)		
C(1)-C(2)-C(3)	119.3(4)	C(8)-C(9)-C(10)	111.9(3)	N(14)-C(15)-O(16)	128.6(4)
C(1)-C(6)-C(5)	120.2(4)	C(8)-C(9)-O(13)	108.3(3)	N(14)-C(15)-N(17)	109.2(3)
C(2)-C(3)-C(4)	120.9(5)	C(9)-C(10)-N(11)	101.1(3)	O(16)-C(15)-N(17)	122.2(4)
C(2)-C(1)-C(6)	120.3(4)	C(10)-N(11)-C(12)	111.6(3)	C(15)-N(17)-C(18)	128.3(4)
C(2)-C(1)-O(7)	124.5(4)	N(11)-C(12)-O(13)	111.5(3)	N(17)-C(18)-O(19)	127.1(4)
C(3)-C(4)-C(5)	119.3(5)	C(12)-O(13)-C(9)	109.5(3)	N(17)-C(18)-O(20)	108.6(4)
C(4)-C(5)-C(6)	120.0(5)	O(13)-C(9)-C(10)	103.6(3)	O(19)-C(18)-O(20)	124.3(4)
C(6)-C(1)-O(7)	115.2(4)	N(11)-C(12)-N(14)	132.8(4)	C(18)-O(20)-C(21)	116.1(4)
C(1)-O(7)-C(8)	116.8(3)	O(13)-C(12)-N(14)	115.8(3)	O(20)-C(21)-C(22)	110.2(5)
O(7)-C(8)-C(9)	106.6(3)	C(12)-N(14)-C(15)	118.7(3)		

Table 4

Final Fractional Coordinates and Equivalent Isotropic Temperature Factors for the Non-hydrogen Atoms of the 2,3,6,7-Tetrahydro-7-phenoxymethyl-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-dione (**2b**)

atom	x	y	z	B_{eq}, Å^2
C(1)	0.8165(1)	0.4164(4)	0.9637(2)	4.4(7)
C(2)	0.7934(1)	0.5037(5)	1.0167(2)	4.7(8)
C(3)	0.8355(1)	0.5669(5)	1.1176(2)	5.5(9)
C(4)	0.9000(2)	0.5421(5)	1.1647(3)	5.9(1)
C(5)	0.9224(1)	0.4553(5)	1.1113(3)	6.0(1)
C(6)	0.8820(1)	0.3919(5)	1.0108(2)	5.1(8)
O(7)	0.7788(8)	0.3498(3)	0.8634(1)	5.2(5)
C(8)	0.7120(1)	0.3609(5)	0.8141(2)	4.7(8)
C(9)	0.6846(1)	0.2521(5)	0.7159(2)	4.9(7)
O(10)	0.6993(7)	0.3460(4)	0.6444(1)	5.3(5)
C(11)	0.6461(1)	0.3784(4)	0.5527(2)	4.2(6)
N(12)	0.6462(9)	0.4490(4)	0.4755(2)	4.4(6)
C(13)	0.5876(1)	0.4669(4)	0.3842(2)	4.4(7)
N(14)	0.5340(9)	0.4217(4)	0.3855(2)	4.4(6)
C(15)	0.5337(1)	0.3426(4)	0.4667(2)	4.4(7)
N(16)	0.5946(8)	0.3231(4)	0.5542(2)	4.1(5)
C(17)	0.6118(1)	0.2396(5)	0.6534(2)	4.9(8)
O(18)	0.5810(8)	0.5192(3)	0.3022(1)	5.3(5)
O(19)	0.4869(8)	0.2943(4)	0.4645(1)	5.6(6)

Table 5

Final Fractional Coordinates and Equivalent Isotropic Temperature Factors for the Non-hydrogen Atoms of the 1-[5-(Phenoxymethyl)-2-iminooxazolidine]-3-carbethoxyurea (**3b**)

atom	x	y	z	B_{eq}, Å^2
C(1)	0.7873(3)	-0.0758(8)	0.3103(2)	3.3(1)
C(2)	0.8516(3)	-0.1020(9)	0.2665(2)	4.2(2)
C(3)	0.9193(3)	-0.2860(1)	0.2818(3)	5.3(2)
C(4)	0.9227(3)	-0.4410(1)	0.3396(3)	5.6(2)
C(5)	0.8569(4)	-0.4140(1)	0.3832(2)	5.7(2)
C(6)	0.7902(3)	-0.2304(9)	0.3687(2)	4.5(2)
O(7)	0.7160(2)	0.0928(5)	0.2994(1)	3.7(1)
C(8)	0.7107(3)	0.2559(8)	0.2394(2)	3.1(1)
C(9)	0.6219(2)	0.3958(7)	0.2337(2)	3.0(1)
C(10)	0.6098(3)	0.5897(7)	0.1729(2)	3.6(2)
N(11)	0.5488(2)	0.4492(6)	0.1183(1)	3.3(1)
C(12)	0.5139(2)	0.2470(7)	0.1444(2)	2.8(1)
O(13)	0.5481(2)	0.2148(5)	0.2130(1)	3.2(1)
N(14)	0.4547(2)	0.0790(6)	0.1171(1)	3.2(1)
C(15)	0.4146(2)	0.1069(8)	0.0491(2)	3.2(1)
O(16)	0.4281(2)	0.2703(6)	0.0069(1)	4.6(1)
N(17)	0.3510(2)	-0.0855(7)	0.0318(2)	4.0(1)
C(18)	0.2897(3)	-0.1139(8)	-0.0285(2)	3.7(2)
O(19)	0.2837(3)	0.0120(7)	-0.0805(4)	6.0(2)
O(20)	0.2344(2)	-0.3045(7)	-0.0198(2)	5.3(1)
C(21)	0.1644(4)	-0.3620(1)	-0.0792(3)	6.7(3)
C(22)	0.0956(4)	-0.5190(2)	-0.0574(3)	8.9(4)

2,3,6,7-tetrahydro-3-methyl-7-phenoxymethyl-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-dione **4i**. N-Alkylation of **2b** was performed at room temperature using a classical procedure [21] leading to compounds **4j-m**. The utility of the fused 1,3,5-triazine-2,4-diones **2** as synthetic intermediates was investigated. In particular, 1-[3-(1-phenoxypropan-2-ol)]-1,3,5-triazine-2,4,6-trione **5n** was easily prepared by a basic hydrolysis of **2b** with 0.2*N* sodium hydroxide at 100°.

Binding *in vitro* studies have been performed for compounds **2b**, **4i** and **4j**, in order to evaluate the interaction with 5-HT_2 receptors. No significant activity was observed.

EXPERIMENTAL

Microanalyses were carried out at the Service central d'analyse CNRS, Vernaison, France. Melting points were determined with a Kofler hot-stage apparatus and were uncorrected. The ir spectra were obtained with a Bruker IF 25 spectrophotometer. The nmr data were recorded with a Bruker AC-200 spectrometer. The study of **3b** was performed on a Bruker AMX-500 spectrometer. Chemical shifts (δ in ppm) and coupling constants (J in Hz) were measured using TMS as the internal standard. Silica gel SDS 60 (70-230 mesh) was used for column chromatography.

Crystal Structure Determinations.

Colourless single crystals of **2b** and **3b** were respectively obtained by slow evaporation from methanol or ethanol solutions. In both cases, the unit cell dimensions were determined using the least-squares fit from 25 reflections ($\theta < 25°$). Intensities were collected with an Enraf-Nonius CAD-4 diffractometer using the CuKα radiation and a graphite monochromator up to $\theta = 70°$ (**2b**) and 65° (**3b**) (scan type ω/θ, scan width 10° and 1.5°). No intensity variation of 2 standard reflections monitored every 90 minutes was observed with both crystals. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. Both structures were determined by the direct methods using MULTAN 80 [22]. The scattering factors were taken from [23]. The C-, N- and O-atoms were refined anisotropically. The H-atoms were placed in theoretical positions or were located from difference *Fourier* maps and were refined isotropically. The convergence largest Δ/σ, were <1 (on Bs), the highest peaks in final difference maps were 0.3 (**2b**) and 0.4 (**3b**) e.Å^{-3}. The atomic coordinates were deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge CB2 IEZ, UK.

General Procedure for the Preparation of 2,3,6,7-Tetrahydro-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-diones **2** and 1-Carbethoxy-3-(2-iminooxazolidine)ureas **3**.

Under vigorous stirring ethoxycarbonyl isocyanate [24] (20 mmoles) was added to a cold solution (0°) of the required 2-amino-2-oxazoline (20 mmoles) in dichloromethane. Then the mixture was stirred three hours at room temperature. The precipitated white solid was collected, washed with dichloromethane and recrystallized to provide compound **2**. After evaporation of the solvent the resulting oil was triturated with ether. The solid obtained was separated and recrystallized to provide **3**.

2,3,6,7-Tetrahydro-7-*t*-butoxymethyl-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-dione (**2a**).

This compound was obtained as a white solid (ethanol), mp 116°, yield 35%; ir (potassium bromide): ν NH 3000, CO 1760, 1700, CN 1634 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 11.25 (s, 1H, N*H*CO), 5.38 (m, 1H, 7-*H*), 4.32 (m, 2H, OCH_2), 4.01 (m, 2H, 6-*H*), 3.74 (s, 9H, $(CH_3)_3$); ^{13}C nmr: δ 164.3 (*C*-9), 157.1 (*C*-4), 147.9 (*C*-2), 79.4 (*C*-7), 74.0 (*C*-$(CH_3)_3$), 61.3 (OCH_2), 43.4 (*C*-6), 27.2 (CH_3).

Anal. Calcd. for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.52; H, 6.30; N, 17.46.

2,3,6,7-Tetrahydro-7-phenoxymethyl-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-dione (**2b**).

This compound was obtained as a white powder (methanol), mp 218°, yield 37%; ir (potassium bromide): ν NH 3440, CO 1750, 1690, CN 1640 cm^{-1}; ^1H nmr (DMSO-d_6): δ 11.34 (s, 1H, N*H*CO), 7.14 (m, 5H, phenyl), 5.44 (m, 1H, 7-*H*), 4.35 (m, 2H, OCH_2), 4.05 (m, 2H, 6-*H*); ^{13}C nmr: δ 164.0 (*C*-9), 157.8 (*C*-4), 148.2 (*C*-2), 156.6, 129.6, 121.3, 114.6 (*C* phenyl), 78.2 (*C*-7), 67.6 (O*C*H_2), 43.2 (*C*-6).

Anal. Calcd. for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.08. Found: C, 55.57; H, 4.48; N, 15.65.

2,3,6,7-Tetrahydro-7-[3-methylphenoxymethyl]-4*H*-oxazolo-[3,2-*a*]1,3,5-triazine-2,4-dione (**2c**).

This compound was obtained as a white solid (ethanol), mp 182°, yield 32%; ir (potassium bromide): ν NH 3200, CO 1738, 1696, CN 1656 cm^{-1}; ^1H nmr (DMSO-d_6): δ 11.30 (s, 1H, N*H*CO), 6.96 (m, 4H, phenyl), 5.37 (m, 1H, 7-*H*), 4.32 (m, 2H, OCH_2), 4.08 (m, 2H, 6-*H*), 2.30 (s, 3H, CH_3); ^{13}C nmr: δ 164.0 (*C*-9), 157.8 (*C*-4), 148.2 (*C*-2), 156.6, 129.4, 122.1, 115.3, 111.5 (*C* phenyl), 78.2 (*C*-7), 67.6 (O*C*H_2), 43.2 (*C*-6), 21.1 (*C*H_3).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.92; H, 4.82; N, 14.98.

2,3,6,7-Tetrahydro-7-[(2,6-dimethylphenoxy)methyl]-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-dione (**2d**).

This compound was obtained as a white solid (ethanol), mp 240°, yield 37%; ir (potassium bromide): ν NH 3400, CO 1750, 1700, CN 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 11.27 (s, 1H, N*H*CO), 6.98 (m, 3H, phenyl), 5.35 (m, 1*H*, 7-*H*), 4.08 (m, 2H, OCH_2), 4.05 (m, 2H, 6-*H*), 2.21 (s, 6H, CH_3); ^{13}C nmr: δ 164.0 (*C*-9), 154.3 (*C*-4), 148.2 (*C*-2), 156.6, 130.4, 128.9, 124.2 (*C* phenyl), 78.9 (*C*-7), 71.2 (O*C*H_2), 43.1 (*C*-6), 15.9 (*C*H_3).

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.27; H, 5.34; N, 14.35.

1-[5-(*t*-Butoxymethyl)-2-iminooxazolidine]-3-carbethoxyurea (**3a**).

This compound was obtained as a white powder (carbon tetrachloride), mp 128°, yield 23%; ir (potassium bromide): ν NH 3360, CO 1764, 1664, CN 1622 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.70 (s, 1H, N*H*CO), 7.42 (s, 1H, N*H*C-4), 4.76 (m, 1H, 5-*H*), 4.18 (q, 2H, CH_2CH$_3$), 3.84 and 3.72 (m, 1H each, 4-*H*), 3.54 (d, 2H, OCH_2), 1.25 (t, 3H, CH$_2$CH_3), 1.14 (s, 9H, (CH_3)$_3$C); ^{13}C nmr: δ 166.8 (N*C*ON), 160.5 (*C*-2), 151.6 (*C*OOCH$_2$CH$_3$), 76.3 (*C*-5), 73.7 ((CH$_3$)$_3$*C*), 61.7 (O*C*H$_2$), 61.4 (*C*H$_2$CH$_3$), 44.7 (*C*-4), 27.3 ((*C*H$_3$)$_3$), 14.2 (*C*H$_3$).

Anal. Calcd for $C_{12}H_{21}N_3O_5$: C, 50.17; H, 7.37; N, 14.62. Found: C, 50.38; H, 7.61; N, 14.32.

1-[5-(Phenoxymethyl)-2-iminooxazolidine]-3-carbethoxyurea (**3b**).

This compound was obtained as a white solid (carbon tetrachloride), mp 150°, yield 21%; ir (potassium bromide): ν NH 3350, CO 1766, 1666, CN 1633 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.83 (s, 1H, N*H*CO), 7.39 (s, 1H, N*H*C-4), 7.04 (m, 5H, phenyl), 5.04 (m, 1H, 5-*H*), 4.21 (q, 2H, CH_2CH$_3$, J = 7.1 Hz), 4.21 (dd, 1H, OCH_{2a}, J = 10.8, 3.9 Hz), 4.17 (dd, 1H, OCH_{2b}, J = 10.8, 4.3 Hz), 4.01 (dd, 1H, 4-H_a, J = 9.4, 5.8 Hz), 3.88 (dd, 1H, 4-H_b, J = 9.4, 6.6 Hz), 1.27 (t, 3H, CH_3, J = 7.1 Hz); ^{13}C nmr: δ 166.3 (N*C*ON), 160.3 (*C*-2), 151.7 (*C*OOCH$_2$CH$_3$), 157.8, 129.5, 121.6, 114.4 (*C* phenyl), 75.2 (*C*-5), 67.3 (O*C*H$_2$), 61.2 (*C*H$_2$CH$_3$), 44.8 (*C*-4), 14.2 (*C*H$_3$).

Anal. Calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.53; H, 5.42; N, 13.61.

1-[5-((3-Methyl)phenoxymethyl)-2-iminooxazolidine]-3-carbethoxyurea (**3c**).

This compound was obtained as colorless needles (trichloroethylene), mp 129°, yield 17%; ir (potassium bromide): ν NH 3360, CO 1778, 1666, CN 1622 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 8.84 (s, 1H, N*H*CO), 7.58 (s, 1H, N*H*C-4), 6.90 (m, 4H, phenyl), 5.02 (m, 1H, 5-*H*), 4.18 (m, 4H, OCH_2 and CH_2CH$_3$), 3.92 (m, 2H, 4-*H*), 2.34 (s, 3H, Ar-CH_3), 1.25 (t, 3H, CH_3); ^{13}C nmr: δ 166.4 (N*C*ON), 160.5 (*C*-2), 151.6 (*C*OOCH$_2$CH$_3$), 157.8, 139.7, 129.3, 122.5, 115.4, 111.3 (*C* phenyl), 75.1 (*C*-5), 67.2 (O*C*H$_2$), 61.4 (*C*H$_2$CH$_3$), 44.7 (*C*-4), 21.4 (phenyl-*C*H$_3$), 14.2 (*C*H$_3$).

Anal. Calcd. for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.07. Found: C, 56.23; H, 6.12; N, 12.83.

1-[5-((2,6-Dimethyl)phenoxymethyl)-2-iminooxazolidine]-3-carbethoxyurea (**3d**).

This compound was obtained as a white solid, mp 130° (trichloroethylene), yield 20%; ir (potassium bromide): ν NH 3397, CO 1770, 1672, CN 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.83 (s, 1H, N*H*CO), 7.39 (s, 1H, N*H*C-4), 6.97 (m, 3H, phenyl), 5.00 (m, 1H, 5-*H*), 4.17 (m, 4H, CH_2CH$_3$), 3.98 (m, 4H, OCH_2 and 4-*H*), 2.25 (s, 6H, Ar-CH_3), 1.26 (t, 3H, CH_3); ^{13}C nmr: δ 66.7 (N*C*ON), 160.4 (*C*-2), 151.5 (*C*OOCH$_2$CH$_3$),154.5, 130.5, 129.0, 124.4 (*C* phenyl), 75.8 (*C*-5), 70.7 (O*C*H$_2$), 61.4 (*C*H$_2$CH$_3$), 44.4 (*C*-4), 16.1 (phenyl-*C*H$_3$), 14.2 (*C*H$_3$).

Anal. Calcd. for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.32; N, 12.53. Found: C, 57.13; H, 6.38; N, 12.53.

2,3,6,7-Tetrahydro-3-methyl-7-phenoxymethyl-4*H*-oxazolo-[3,2-*a*]-1,3,5-triazine-2,4-dione (**4i**).

A solution of compound **2b** (4 mmoles) in dry toluene (50 ml) and *N,N*-dimethylformamide dimethylacetal (10 mmoles) was refluxed with protection from moisture. After 5 hours, the solvent and the excess of reagent were distilled under reduced pressure leading to an oil. It was chromatographied over silica gel and the column eluted with chloroform-methanol (9/1) as the eluent to provide **4i** which was crystallized from toluene in 62% yield, mp 176°; ir (potassium bromide): ν CO 1745, 1680, CN 1634 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.16 (m, 5H, phenyl), 5.45 (m, 1H, 7-*H*), 4.35 (m, 2H, OCH_2), 3.95 (m, 2H, 6-*H*), 3.15 (s, 3H, CH_3); ^{13}C nmr: δ 162.4 (*C*-9), 157.8 (*C*-4), 148.5 (*C*-2), 155.9, 129.6, 121.3, 114.6 (*C* phenyl), 78.3 (C-7), 67.6 (O*C*H_2), 44.0 (*C*-6), 28.2 (*C*H_3).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.57; H, 4.79; N, 15.09.

General Procedure for the Preparation of 2,3,6,7-Tetrahydro-3-alkyl-7-phenoxymethyl-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-diones **4j-m**.

To a suspension of anhydrous potassium carbonate (7.6 mmoles) in dry DMSO was added 3.8 mmoles of compound **2b**. The mixture was stirred 30 minutes and the bromo compound (4.6 mmoles) was added. The stirring was continued 12 hours. Then, water (100 ml) was added and the mixture was neutralized to *p*H = 7 with 0.1*N* hydrochloric acid. The precipitated white solid was filtered to provide unreacted compound **2b**. The

solution was concentrated. The residue was chromatographed on a silica gel column, eluted with chloroform-heptane (50/50) to give compounds **4j-m**.

2,3,6,7-Tetrahydro-3-benzyl-7-phenoxymethyl-4*H*-oxazolo-[3,2-*a*]-1,3,5-triazin-2,4-dione (**4j**).

This compound was obtained from **2a** in 53% yield, mp 168° (methanol); ir (potassium bromide): ν CO 1740, 1680, CN 1659 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.51 (m, 10H, phenyl), 5.40 (m, 1H, 7-*H*), 5.28 (s, 2H, phenyl-CH_2), 4.36 (m, 2H, OCH_2), 4.25 (dd, 1H, 6-H_a, J = 10.9, 3.2 Hz), 3.97 (dd, 1H, 6-H_b, J = 10.9, 3.1 Hz); ^{13}C nmr: δ 162.6 (*C*-9), 157.8 (*C*-4), 148.5 (*C*-2), 155.5, 136.8, 129.6, 128.3, 127.6, 127.3, 121.3, 114.6 (*C* phenyl), 78.6 (*C*-7), 67.6 (O*C*H_2), 44.4 (Ar-*C*H_2), 44.1 (*C*-6).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.82; H, 4.61; N, 11.88.

2,3,6,7-Tetrahydro-3-allyl-7-phenoxymethyl-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-dione (**4k**).

This compound was obtained from **2a** in 43% yield, mp 173° (methanol); ir (potassium bromide): CO 1740, 1670, CN 1620 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.14 (m, 5H, Ar-*H*), 5.83 (m, 1H, C*H*=CH$_2$), 5.41 (m, 1H, 7-*H*), 5.16 (m, 2H, CH_2-CH), 5.10 (s, 2H, CH=CH_2), 4.34 (m, 2H, OCH_2), 4.24 (dd, 1H, 6-H_a, J = 11.9, 3.3 Hz), 3.95 (dd, 1H, 6-H_b, J = 11.9, 5.2 Hz); ^{13}C nmr: δ 162.5 (*C*-9), 158.0 (*C*-4), 148.1 (*C*-2), 155.2, 129.6, 121.8, 115.0 (*C* phenyl), 132.3 (*C*H=CH$_2$), 116.8 (CH=*C*H_2), 78.6 (*C*-7), 67.3 (O*C*H_2), 44.0 (*C*H_2-CH), 43.3 (*C*-6).

Anal. Calcd. for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 5.02; N, 13.94. Found: C, 59.84; H, 4.82; N, 13.90.

2,3,6,7-Tetrahydro-3-phenacyl-7-phenoxymethyl-4*H*-oxazolo-[3,2-*a*]-1,3,5-triazine-2,4-dione (**4l**).

This compound was obtained from **2a** in 21% yield, mp 226° (methanol); ir (potassium bromide): ν CO 1745, 1700, 1660, CN 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.49 (m, 10H, phenyl), 5.52 (m, 1H, 7-*H*), 5.29 (s, 2H, CH_2CO), 4.39 (d, 2H, OCH_2, J = 8.1 Hz), 4.32 (dd, 1 H, 6-H_a, J = 10.8, 3.2 Hz), 4.07 (dd, 1*H*, 6-H_b, J = 10.8, 5.6 Hz); ^{13}C nmr: δ 192.3 (*C*=O), 162.9 (*C*-9), 157.8 (*C*-4), 148.7 (*C*-2), 155.3, 135.3, 134.0, 129.6, 129.1, 128.0, 121.3, 114.6 (*C* phenyl), 78.9 (*C*-7), 67.6 (O*C*H_2), 47.8 (*C*H_2-CO), 44.0 (*C*-4).

Anal. Calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.55; H, 4.35; N, 10.99.

2,3,6,7-Tetrahydro-3-[(2,3-epoxy)propan]-7-phenoxymethyl-4*H*-oxazolo[3,2-*a*]-1,3,5-triazine-2,4-dione (**4m**).

This compound was obtained from **2a** in 31% yield, mp 166° (methanol); ir (potassium bromide): ν CO 1740, 1680, CN 1620 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.05 (m, 5H, phenyl), 5.38 (m, 1H, 7-*H*), 4.38 (dd, 1H, OCH_{2a}, J = 11.2, 3.3 Hz), 4.24 (dd, 1H, OCH_{2b}, J = 11.2, 3.2 Hz), 4.10 (m, 2H, N-CH_2-CH, J = 5.1, 3.7 Hz), 4.08 (dd, 1H, 6-H_a, J = 11.8, 3.7 Hz), 4.00 (dd, 1H, 6-H_b, J = 11.8, 4.5 Hz), 3.26 (m, 1H, CH$_2$-C*H*-CH$_2$), 2.78 (dd, 1H, CH-CH_{2a}, J = 4.7, 1.8 Hz), 2.72 (dd, 1H, CH-CH_{2b}, J = 4.7, 2.1 Hz); ^{13}C nmr: δ 162.6 (*C*-9), 157.8 (*C*-4), 148.4 (*C*-2), 155.6, 129.6, 121.1, 114.6 (*C* phenyl), 78.5 (*C*-7), 67.6 (O*C*H_2), 48.6 (*C*H-CH$_2$), 45.2 (N-*C*H_2-CH), 44.0 (*C*-6), 42.7 (CH-*C*H_2).

Anal. Calcd. for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.76; N, 13.24. Found: C, 56.66; H, 4.81; N, 13.24.

1-[3-(1-Phenoxypropan-2-ol)]-1,3,5-triazine-2,4,6-trione (**5n**).

A stirred solution of compound **2b** (0.5 g, 1.9 mmoles) in 30 ml of 0.2*N* sodium hydroxide was refluxed during 2 hours, then the clear solution was cooled at room temperature and it was acidified with 1*N* hydrochloric acid to *p*H = 5. The precipitate was collected by filtration, washed with water, dried and recrystallized from ethanol to provide analytically pure **5n** (0.4 g, 75%), mp 224°; ir (potassium bromide): ν NH 3449, OH 3240, CO 1768, 1735, 1693 cm^{-1}; ^1H nmr (DMSO-d_6): δ 11.36 (s, 2H, N*H*), 7.08 (m, 5H, phenyl), 5.32 (d, 1H, OH, J = 5.2 Hz), 4.15 (m, 1H, CH), 3.85 (m, 2H, OCH_2), 4.79 (dd, 1H, CH_{2a}N, J = 13.3, 3.8 Hz), 3.68 (dd, 1H, CH_{2b}N, J = 13.3, 5.9 Hz); ^{13}C nmr: δ 163.1 (*C*-6) 150.1 (*C*-2 and *C*-4), 148.8, 129.5, 120.6, 114.4 (*C* phenyl), 70.4 (*C*H), 65.6 (O*C*H_2), 43.8 (*C*H_2N).

Anal. Calcd. for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.10. Found: C, 51.72; H, 4.83; N, 14.92.

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