

**REACTION OF 4-BROMOBENZYL-3-METHYL-1,2-OXAZIN-6-ONES
WITH PRIMARY ALIPHATIC AMINES. SYNTHESIS AND
STRUCTURAL DETERMINATION OF NEW OXAZINE AND
ISOXAZOLE DERIVATIVES**

Monique Bebot,^a Pascal Coudert,^a Fernand Leal,^a Jacques Métin,^b Vincent Gaumet,^b Sylvie Mavel,^d Catherine Rubat,^c and Jacques Couquelet^{a*}

^aLaboratoire de Chimie Thérapeutique; ^bLaboratoire de Chimie Physique et Minérale; ^cLaboratoire de Pharmacologie, Groupe de Recherche en Pharmacochimie, UFR de Pharmacie, 28 Place Henri Dunant, BP 38, 63001 Clermont-Ferrand Cedex, France ; ^dLaboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques, Université François Rabelais, Avenue Monge, 37200 Tours, France

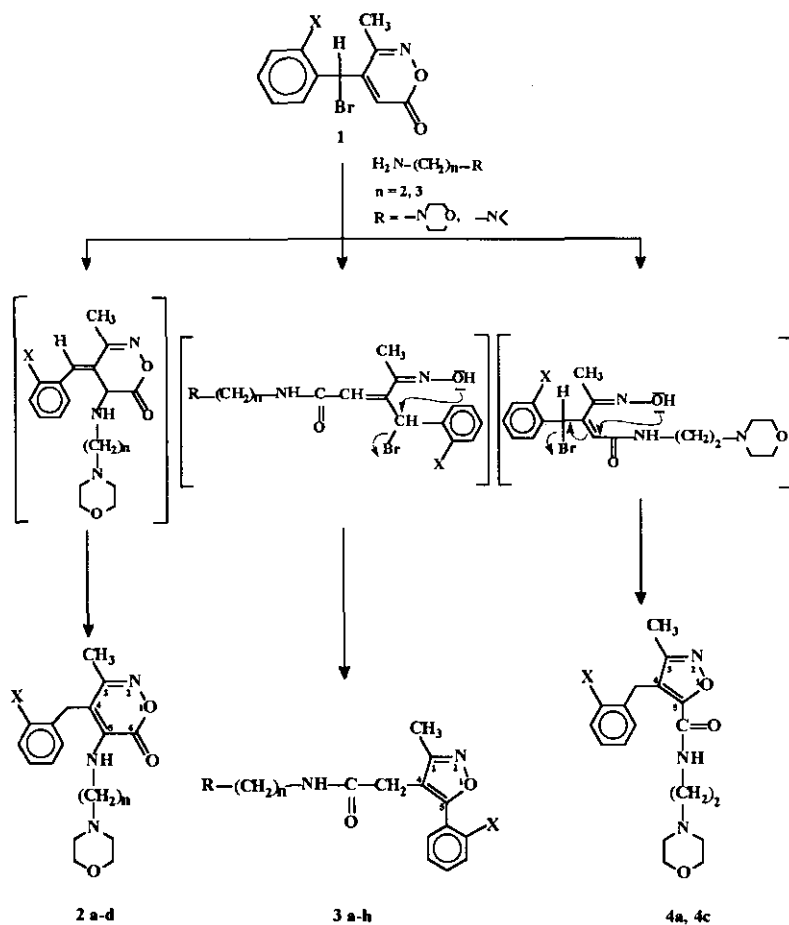
Abstract - Reaction of 4-bromobenzyl-6H-1,2-oxazin-6-ones (1) with aminoalkylamines furnished a mixture of 5-aminoalkylamino-6H-1,2-oxazin-6-ones (2), 4-(aminoalkylaminocarbonylmethyl)isoxazoles (3) and 5-(Aminoalkylaminocarbonyl)isoxazoles (4) which were separated by column chromatography. Structure of all derivatives was determined by ¹H- and ¹³C-NMR methods, including INEPT measurements. Structure of isoxazoles (3) and (4) was confirmed by X-Ray analysis. In addition, test compounds were investigated for analgesic and antidepressant activities in mice.

In earlier experiments, we prepared several compounds by substitution of 4-bromobenzyl-6H-1,2-oxazin-6-ones with arylpiperazines. The aim of these investigations was the synthesis of new analgesic derivatives.¹ We extended the application of the above reaction to different diamines : morpholinoalkylamines and dimethylaminoalkylamines. Introduction of these amino groups into pharmacophoric nuclei often produced biologically active compounds, such as analgesics^{2,3} or antidepressants.⁴⁻⁶ While the action of arylpiperazines led to a sole type of derivatives, primary amines yielded three different compounds due to rearrangements. As part of our studies, we describe here the

synthesis of new 1,2-oxazine and isoxazole derivatives. Their structures were established on the basis of spectral data and were confirmed by X-Ray measurements.

SYNTHESIS

Starting 4-bromobenzyl-3-methyl-1,2-oxazin-6-ones (**1**) were prepared according to a previously described procedure.¹ Reaction of diamines with **1** in methanolic solution gave rise to a mixture of three derivatives as shown in Scheme 1. The ratio of products (**2**, **3** and **4**) depends on the employed bases. Thus, dimethylaminoalkylamines furnished only compounds (**3**), whereas morpholinoalkylamines led to the three different compounds. Formation of 5-substituted 1,2-oxazinones (**2**) (Tables 1-3) involved an S_N2' mechanism without intramolecular rearrangement. Isoxazoles (**3**) (Tables 4-6) and (**4**) (Tables 7-9) were generated through an opening of the oxazine ring by amines, leading to an oxime intermediate. Further cyclisation occurred by S_N2 and S_N2' mechanisms for **3** and **4** respectively.



Scheme 1

Table 1. Yield, physical and analytical data for derivatives (2a-d).

Compd	X	n	Yield (%)	mp (°C)	Formula	Analysis % Calcd (Found)			
						C	H	N	Cl
2a	H	2	18	71-74	C ₁₈ H ₂₃ N ₃ O ₃	65.63 (65.42)	7.04 (7.18)	12.76 (12.49)	
2b	H	3	8	71-83	C ₁₉ H ₂₅ N ₃ O ₃	66.44 (66.72)	7.34 (7.28)	12.24 (12.15)	
2c	Cl	2	5	yellow oil	C ₁₈ H ₂₂ N ₃ O ₃ Cl	59.42 (59.21)	6.10 (6.33)	11.55 (11.63)	9.74 (9.81)
2d	Cl	3	16	yellow oil	C ₁₉ H ₂₄ N ₃ O ₃ Cl	60.39 (60.38)	6.40 (6.72)	11.12 (11.14)	9.38 (9.20)

Table 2. Characteristic IR frequencies and ¹H-NMR chemical shifts of derivatives (2a-d).

Compd	IR (cm ⁻¹ , KBr)		¹ H-NMR (CDCl ₃ , δ, ppm)
	ν N-H	ν C=O	
2a	3630-3240	1700	2.16 (3H, s, CH ₃), 2.37 (4H, t, \underline{J} = 4.5 Hz, 2 CH ₂ morph.), 2.48 (2H, t, \underline{J} = 5.9 Hz, CH ₂), 3.63 (2H, dt, \underline{J} = 5.9 and 4.8 Hz, CH ₂), 3.83 (4H, t, \underline{J} = 4.5 Hz, 2 CH ₂ morph.), 3.92 (2H, s, CH ₂ -C ₆ H ₅), 6.02 (1H, t, \underline{J} = 4.7 Hz, N-H), 7.15-7.39 (5H, m, C ₆ H ₅)
2b	3660-3160	1695	1.68 (2H, quint, \underline{J} = 6.2 Hz, CH ₂), 2.06 (3H, s, CH ₃), 2.38-2.41 (6H, m, CH ₂ +2 CH ₂ morph.), 3.53 (2H, t, \underline{J} = 6.2 Hz, CH ₂), 3.68 (4H, t, \underline{J} = 4.6 Hz, 2 CH ₂ morph.), 3.93 (2H, s, CH ₂ -C ₆ H ₅), 6.77 (1H, br s, N-H), 7.12-7.33 (5H, m, C ₆ H ₅)
2c	3620-3120	1695	2.11 (3H, s, CH ₃), 2.33 (4H, t, \underline{J} = 4.5 Hz, 2 CH ₂ morph.), 2.44 (2H, t, \underline{J} = 5.8 Hz, CH ₂), 3.48 (2H, dt, \underline{J} = 5.8 and 5.0 Hz, CH ₂), 3.58 (4H, t, \underline{J} = 4.5 Hz, 2 CH ₂ morph.), 3.89 (2H, s, CH ₂ -C ₆ H ₄), 6.02 (1H, br s, N-H), 6.93-7.47 (4H, m, C ₆ H ₄)
2d	3700-3100	1695	1.68 (2H, quint, \underline{J} = 6.2 Hz, CH ₂), 2.06 (3H, s, CH ₃), 2.40-2.43 (6H, m, CH ₂ +2 CH ₂ morph.), 3.43 (2H, t, \underline{J} = 6.2 Hz, CH ₂), 3.71 (4H, t, \underline{J} = 4.7 Hz, 2 CH ₂ morph.), 3.94 (2H, s, CH ₂ -C ₆ H ₄), 6.90 (1H, br s, N-H), 6.98-7.45 (4H, m, C ₆ H ₄)

Table 3. ¹³C-NMR chemical shifts of derivatives (2a-d).

Compd	CH ₃	CH ₂ benz.	(CH ₂) _n	CH ₂ morph.	C(4)	Ar	C(5)	C=N	C=O
2a	17.9	32.2	40.6, 57.1	52.9, 66.8	107.6	127.0-137.0	137.4	156.3	163.3
2b	17.9	32.5	25.9, 44.8, 57.2	53.8, 66.5	106.1	126.9-138.2	137.2	156.7	164.3
2c	17.7	30.3	40.4, 57.1	52.9, 66.7	105.9	127.4-134.9	137.3	156.2	163.7
2d	17.5	30.4	25.7, 44.3, 57.0	53.6, 66.3	104.4	127.4-135.8	137.4	156.5	164.0

Table 4. Yield, physical and analytical data for derivatives (3a-h).

Compd	X	R	n	Yield (%)	mp (°C)	Formula	Analysis % Calcd (Found)			
							C	H	N	Cl
3a	H		2	33	119-123	C ₁₈ H ₂₃ N ₃ O ₃	65.63 (65.45)	7.04 (6.92)	12.76 (13.01)	
3b	H		3	58	150-162	C ₁₉ H ₂₅ N ₃ O ₃	66.44 (66.75)	7.34 (7.16)	12.24 (12.16)	
3c	Cl		2	22	93-101	C ₁₈ H ₂₂ N ₃ O ₃ Cl	59.42 (59.25)	6.10 (6.37)	11.55 (11.72)	9.74 (9.82)
3d	Cl		3	39	brown oil	C ₁₉ H ₂₄ N ₃ O ₃ Cl	60.39 (60.32)	6.40 (6.71)	11.12 (11.23)	9.38 (9.02)
3e	H		2	28	111-115	C ₁₆ H ₂₁ N ₃ O ₂	66.87 (66.47)	7.37 (7.24)	14.63 (14.85)	
3f	H		3	24	102-105	C ₁₇ H ₂₃ N ₃ O ₂	67.74 (68.01)	7.69 (7.48)	13.95 (14.05)	
3g	Cl		2	19	yellow oil	C ₁₆ H ₂₀ N ₃ O ₂ Cl	59.71 (59.57)	6.26 (6.21)	13.06 (13.31)	11.02 (10.69)
3h	Cl		3	31	yellow oil	C ₁₇ H ₂₂ N ₃ O ₂ Cl	60.80 (60.51)	6.60 (6.75)	12.52 (12.84)	10.56 (10.37)

Table 5. Characteristic IR frequencies and ¹H-NMR chemical shifts of derivatives (3a-h).

Compd	IR (cm ⁻¹ , KBr)		¹ H-NMR (CDCl ₃ , δ, ppm)
	ν N-H	ν C=O	
3a	3660-3140	1645	2.32-2.33 (7H, m, CH ₃ +2 CH ₂ morph.), 2.41 (2H, t, <i>J</i> = 5.9 Hz, CH ₂), 3.34 (2H, dt, <i>J</i> = 5.9 and 4.9 Hz, CH ₂), 3.51-3.53 (6H, m, CH ₂ +2 CH ₂ morph.), 6.45 (1H, br s, N-H), 7.46-7.71 (5H, m, C ₆ H ₅)
3b	3660-3160	1635	1.71 (2H, quint, <i>J</i> = 6.6 Hz, CH ₂), 2.34 (3H, s, CH ₃), 2.40-2.44 (6H, m, CH ₂ +2 CH ₂ morph.), 3.38 (2H, dt, <i>J</i> = 6.6 and 5.1 Hz, CH ₂), 3.54 (2H, s, CH ₂ -C=O), 3.65 (4H, t, <i>J</i> = 4.6 Hz, 2 CH ₂ morph.), 6.80 (1H, t, <i>J</i> = 4.8 Hz, N-H), 7.49-7.71 (5H, m, C ₆ H ₅)
3c	3540-3140	1650	2.33 (3H, s, CH ₃), 2.46-2.50 (6H, m, CH ₂ +2 CH ₂ morph.), 3.32-3.36 (4H, m, CH ₂ + CH ₂ -C=O), 3.66 (4H, t, <i>J</i> = 4.5 Hz, 2 CH ₂ morph.), 6.56 (1H, br s, N-H), 7.36-7.52 (4H, m, C ₆ H ₄)
3d	3700-3150	1645	1.67 (2H, m, CH ₂), 2.24 (3H, s, CH ₃), 2.47-2.53 (6H, m, CH ₂ +2 CH ₂ morph.), 3.20-3.23 (4H, m, CH ₂ +CH ₂ -C=O), 3.64 (4H, t, <i>J</i> = 4.5 Hz, 2 CH ₂ morph.), 7.17 (1H, br s, N-H), 7.31-7.43 (4H, m, C ₆ H ₄)
3e	3600-3240	1645	2.11 (6H, s, N(CH ₃) ₂), 2.30-2.33 (5H, m, CH ₃ +CH ₂), 3.29 (2H, dt, <i>J</i> = 5.9 and 5.2 Hz, CH ₂), 3.48 (2H, s, CH ₂ -C=O), 6.30 (1H, br s, N-H), 7.42-7.70 (5H, m, C ₆ H ₅)
3f	3360-3140	1645	1.54 (2H, quint, <i>J</i> = 5.6 Hz, CH ₂), 1.90 (6H, s, N(CH ₃) ₂), 2.27-2.31 (5H, m, CH ₃ +CH ₂), 3.38 (2H, dt, <i>J</i> = 5.6 and 4.7 Hz, CH ₂), 3.50 (2H, s, CH ₂ -C=O), 7.45-7.69 (5H, m, C ₆ H ₅), 8.33 (1H, br s, N-H)
3g	3620-3140	1650	2.17 (6H, s, N(CH ₃) ₂), 2.31-2.37 (5H, m, CH ₃ +CH ₂), 3.25-3.30 (4H, m, CH ₂ +CH ₂ -C=O), 6.40 (1H, br s, N-H), 7.33-7.51 (4H, m, C ₆ H ₄)
3h	3620-3120	1650	1.33 (2H, quint, <i>J</i> = 6.4 Hz, CH ₂), 1.82 (6H, s, N(CH ₃) ₂), 1.97-2.05 (5H, m, CH ₃ +CH ₂), 2.98-3.02 (4H, m, CH ₂ +CH ₂ -C=O), 7.07-7.27 (4H, m, C ₆ H ₄), 7.64 (1H, t, <i>J</i> = 4.9 Hz, N-H)

Table 6. ^{13}C -NMR chemical shifts of derivatives (3a-h).

Compd	CH_3	$\text{N}(\text{CH}_3)_2$	$\text{C}_\alpha\text{H}_2\text{-C=O}$	$(\text{CH}_2)_n$	CH_2 morph.	C(4)	Ar	C=N	C(5)	C=O
3a	10.2	—	31.0	35.6, 56.6	53.0, 66.7	107.7	126.7-130.2	160.7	166.4	168.7
3b	10.3	—	31.1	24.9, 39.0, 57.1	53.6, 66.5	107.8	126.9-130.3	160.9	166.6	169.0
3c	10.2	—	30.3	35.4, 56.6	52.9, 66.3	110.8	126.7-133.2	160.0	164.8	168.5
3d	10.3	—	30.1	24.4, 38.0, 56.3	52.9, 65.7	111.0	126.6-133.1	160.1	164.6	168.8
3e	10.2	45.0	31.0	37.0, 57.6	—	107.8	127.0-130.1	160.8	166.7	168.9
3f	10.1	44.8	31.2	24.3, 41.2, 59.7	—	107.7	126.6-130.0	160.8	167.0	169.0
3g	10.2	44.9	30.4	36.8, 57.5	—	111.0	126.9-133.5	160.1	164.9	168.7
3h	9.7	44.5	29.7	25.2, 38.9, 57.7	—	110.6	126.3-132.8	159.6	164.3	168.4

Table 7. Yield, physical and analytical data for derivatives (4a) and (4c).

Compd	X	n	Yield (%)	mp (°C)	Formula	Analysis % Calcd. (Found)			
						C	H	N	Cl
4a	H	2	28	yellow oil	$\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_3$	65.63 (65.51)	7.04 (7.19)	12.76 (13.01)	
4c	Cl	2	10	96-108	$\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_3\text{Cl}$	59.42 (59.05)	6.10 (6.47)	11.55 (11.43)	9.74 (9.79)

Table 8. Characteristic IR frequencies and ^1H -NMR chemical shifts of derivatives (4a) and (4c).

Compd	IR (cm^{-1} , KBr)		^1H -NMR (CDCl_3 , δ , ppm)
	ν N-H	ν C=O	
4a	3680-3120	1660	2.15 (3H, s, CH_3), 2.53 (4H, t, $J = 4.6$ Hz, 2 CH_2 morph.), 2.62 (2H, t, $J = 6.0$ Hz, CH_2), 3.55 (2H, dt, $J = 6.0$ and 5.4 Hz, CH_2), 3.75 (4H, t, $J = 4.6$ Hz, 2 CH_2 morph.), 4.17 (2H, s, $\text{C}_\alpha\text{H}_2\text{-C}_6\text{H}_5$), 7.18-7.30 (6H, m, N-H+ C_6H_5)
4c	3560-3260	1670	2.09 (3H, s, CH_3), 2.52 (4H, t, $J = 4.6$ Hz, 2 CH_2 morph.), 2.60 (2H, t, $J = 6.0$ Hz, CH_2), 3.54 (2H, dt, $J = 6.0$ and 5.2 Hz, CH_2), 3.74 (4H, t, $J = 4.6$ Hz, 2 CH_2 morph.), 4.31 (2H, s, $\text{C}_\alpha\text{H}_2\text{-C}_6\text{H}_4$), 7.01-7.38 (5H, m, N-H+ C_6H_4)

Table 9. ^{13}C -NMR chemical shifts of derivatives (4a) and (4c).

Compd	CH_3	CH_2 benz.	$(\text{CH}_2)_n$	CH_2 morph.	C(4)	Ar	C(5)	C=O	C=N
4a	10.4	28.1	35.4, 56.7	53.3, 66.8	121.2	126.6-138.3	157.0	157.4	161.7
4c	10.2	25.4	35.4, 56.7	53.3, 66.8	119.8	126.9-135.6	157.7	157.2	161.8

SPECTROSCOPIC INVESTIGATIONS AND X-RAY DETERMINATION

The ^1H -NMR data and most characteristic IR frequencies of compounds (2, 3 and 4) are listed in Tables 2, 5 and 8, and ^{13}C -NMR lines in Tables 3, 6 and 9. Principal ^1H - ^{13}C long-range correlations determined by a selective INEPT experiment (Insensitive Nuclei Enhanced by Polarisation Transfer) are listed in Table 10. For derivatives (2), spectral data are comparable to those previously reported.¹ In the case of compounds (3) and (4), their amidic structure has been established essentially on the basis of ^1H - ^{13}C long-range correlations. For example, INEPT spectrum of **3c** showed long-range correlations between carbonyl group at 168.5 ppm and both N-H signal at 6.6 ppm and $\text{CH}_2\text{-C}(4)$ at 3.32 ppm. But no correlation was found between aromatic carbons and $\text{CH}_2\text{-C}(4)$. On the contrary, INEPT spectrum of **4c** showed a long-range correlation between aromatic carbons and $\text{CH}_2\text{-C}(4)$ at 4.31 ppm, but no correlation between carbonyl group at 157.2 ppm and $\text{CH}_2\text{-C}(4)$. In addition, a long-range correlation was observed between carbonyl group and N-H signal at 7.38 ppm. Structures of **3c** and **4c** were confirmed by their crystallographic data. Projection of both molecules obtained with the ORTEP-III program⁷ are given in Figure 1.

Table 10. ^1H - ^{13}C long-range correlations in the INEPT spectra of compounds (2, 3 and 4).

Irradiated protons	Comps 2	Comps 3	Comps 4
CH_3	C=N, C(4)	C=N, C(4)	C=N, C(4)
$\text{CH}_2\text{-C}(4)$	C(4), Ar, C(5), C=N	C=O, C(4), C=N, C(5)	C(4), Ar, C(5), C=N
$\text{CH}_2\text{-NH}$	C(5)	C=O	C=O
NH	C(4), C=O	C=O	C=O
Ar ortho	$\text{CH}_2\text{-C}(4)$, Ar	C(5), Ar	$\text{CH}_2\text{-C}(4)$, Ar

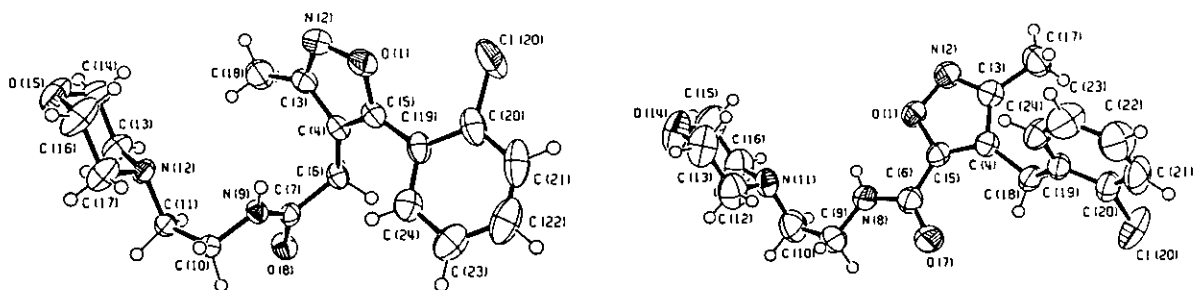


Figure 1. ORTEP drawings of **3c** (left) and **4c** (right) showing 50 % probability displacement ellipsoids

PHARMACOLOGICAL STUDIES

Following our search for new antinociceptive agents, we first investigated derivatives (2) for analgesic properties in the phenylbenzoquinone-induced writhing test,⁸⁻⁹ since they share structural similarities with previously described¹ arylpiperazinyloxazinones effective in this field. Unfortunately 1,2-oxazinones (2) exhibited a weak activity causing around 20 % decrease of visceral pain at the dose of 100 mg/kg i.p. In the same conditions, isoxazoles (3) and (4) were also devoid of potent antinociceptive effect. Furthermore, compounds (2, 3 and 4) did not present any significant antidepressant activity at 100 mg/kg i.p. in the forced swimming test¹⁰ as well as in the reserpine-induced palpebral ptosis test.¹¹⁻¹²

EXPERIMENTAL

All chemicals were obtained from Janssen Chimica, Noisy-le-Grand, France. Melting points were determined on a Reichert apparatus without correction. IR spectra were recorded on a Beckman 4240 spectrophotometer. NMR spectra were obtained on a Bruker AC 400 MHz. The chemical shifts were reported in parts per million (δ , ppm) downfield from tetramethylsilane, used as an internal standard for CDCl₃ solution. The NMR signals were designated as follows : s, singlet; t, triplet; quint, quintet; m, multiplet; dt, doublet of triplets. INEPT spectra were run by using the standard Bruker program INEPTDN.AU. Reaction progress and purity of products were checked by analytical TLC using silicagel plates (60-25 + F254, SDS, Peypin, France). Spots were visualized with UV 254 light. Column chromatography was performed with Silice A.C.C. 60, Chromagel (35-70 μ m, SDS). Microanalyses were performed by the Service Central d' Analyses du CNRS, Vernaison, France, and the analytical results obtained were within ± 0.4 % of the theoretical values.

Preparation of 4-benzyl-3-methyl-5-(*N*-morpholinoalkylamino)-6-oxo-6*H*-1,2-oxazines 2, 5-aryl-3-methyl-4-(aminoalkylaminocarbonylmethyl)isoxazoles 3 and 4-benzyl-3-methyl-5-(*N*-morpholinoethylaminocarbonyl)isoxazoles 4.

The appropriate diamine (10 mmol) was added to a solution of α -bromobenzyl-6*H*-1,2-oxazin-6-one (1) (5 mmol) in methanol (30 mL). The mixture was stirred at 0°C for 3 h. After evaporation the residue was triturated in an aqueous solution of 1N NaHCO₃ (30 mL), and extracted with chloroform (3 \times 30 mL). The organic layer was dried over sodium sulfate and after evaporation, the residue was purified by column chromatography (eluent : ethyl acetate-cyclohexane, 40:60 to collect the first fraction, and then a gradient of ethyl acetate - methanol mixture for the following fractions).

Table 11. Experimental details for structures (3c) and (4c).

	3c	4c
Crystal data		
Formula	C ₁₈ H ₂₂ N ₃ O ₃ Cl	C ₁₈ H ₂₂ N ₃ O ₃ Cl
Fw	363.85	363.85
Color, form	Colorless, prism	Colorless, prism
Crystal size (mm)	0.35 × 0.45 × 0.50	0.08 × 0.37 × 0.42
Symmetry	Orthorhombic	Monoclinic
Space group	Pna2 ₁	P2 ₁ /c
<i>a</i> (Å)	10.211(2)	15.738(5)
<i>b</i> (Å)	22.346(3)	7.275(1)
<i>c</i> (Å)	8.032(2)	17.489(2)
β (°)		111.59(2)
<i>V</i> (Å ³)	1832.7(9)	1861.9
<i>Z</i>	4	4
<i>D</i> _{calc} (g·cm ⁻³)	1.32	1.30
<i>F</i> (000)	768	768
Data collection		
θ limits (°)	1 ≤ θ ≤ 35	1 ≤ θ ≤ 30
Nber. of measured reflections	4249	4490
Nber. of independant reflections	4249	4490
Nber. of observed reflections with $I \geq 1.5 \sigma(I)$	2666	2130
Standard reflections	3	3
Frequency (s)	3600	3600
Intensity decay	2 %	2 %
Data collected	0 ≤ <i>h</i> ≤ 16 0 ≤ <i>k</i> ≤ 36 0 ≤ <i>l</i> ≤ 12	-25 ≤ <i>h</i> ≤ 25 0 ≤ <i>k</i> ≤ 11 0 ≤ <i>l</i> ≤ 28
Refinement on <i>F</i>		
Final <i>R</i>	0.045	0.053
ωR	0.039	0.051
<i>S</i>	2.04	1.69
Nber. of reflections	2665	2118
Nber. of parameters	314	315
ω	1/ $\sigma^2(F)$	1/ $\sigma^2(F)$
(Δ/σ) _{max}	0.01	0.01
Max. and min. electron density in final Fourier difference map (e Å ⁻³)	0.24 -0.28	0.20 -0.19
Extinction coefficient <i>g</i> ^a	5.86 × 10 ⁻⁷	1.79 × 10 ⁻⁷

$$^a F_c = |E_c| (1 + g I_c)^{-16}$$

X-Ray analyses of 3c and 4c

Compounds **3c** and **4c** were crystallized from ethanol to give single crystals. X-Ray crystallographic data collections were carried out at room temperature on a Enraf-Nonius CAD-4 diffractometer with graphite monochromated MoK α radiation ($\lambda = 0.71069$ Å). Crystals data are listed in Table 11. Lattice parameters were obtained by least-squares refinement of 25 reflections with $8 < \theta < 20^\circ$. The intensity data were collected in an $\theta - 2\theta$ scan mode without absorption correction. All calculations were performed with the crystallographic software package MolEN.¹³ Atomic scattering factors and anomalous dispersion

correction were taken from International Tables for X-Ray Crystallography.¹⁴ Structures were solved by direct methods using MULTAN 11/82.¹⁵ All non-H atoms were located in the initial E-map and refined anisotropically using a full-matrix least-squares method. H-atom parameters were refined isotropically.

ACKNOWLEDGMENT

The authors wish to thank Professor Tibor Liptaj for his collaboration in NMR experiences.

REFERENCES

1. M. Bebot, P. Coudert, C. Rubat, D. Vallee-Goyet, D. Gardette, S. Mavel, E. Albuissou, and J. Couquelet, *Chem. Pharm. Bull.*, 1997, **45**, 659.
2. C.G. Wermuth, G. Leclerc, and P. Melounou, *Chim. Ther.*, 1970, **5**, 243.
3. M.C. Viaud, P. Jamoneau, C. Flouzat, J.G. Bizot-Espiard, B. Pfeiffer, P. Renard, D.H. Caignard, G. Adam, and G. Guillaumet, *J. Med. Chem.*, 1995, **38**, 1278.
4. J.P. Yardley, G. E. Morris Husbands, G. Stack, J. Butch, J. Bicksler, J.A. Moyer, E.A. Muth, T. Andree, H. Fletcher, M.N.G. James, and A.R. Sielecki, *J. Med. Chem.*, 1990, **33**, 2899.
5. D. Giannotti, G. Viti, P. Sbraci, V. Pestellini, G. Volterra, F. Borsini, A. Lecci, A. Meli, P. Dapporto, and P. Paoli, *J. Med. Chem.*, 1991, **34**, 1356.
6. T. Nakagawa, K. Ukai, and S. Kubo, *Arzneim.-Forsch./Drug Res.*, 1993, **43**, 11.
7. M.N. Burnett and C.K. Johnson, 'ORTEP III', report ORNL-6895, Oak Ridge National Laboratory, Tennessee, USA, 1996.
8. E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, 1957, **95**, 729.
9. P. Linee, *J. Pharmacol.* (Paris), 1972, **3**, 513.
10. R.D. Porsolt, A. Bertin, and M. Jalfre, *Arch. Int. Pharmacodyn.*, 1977, **229**, 327.
11. C. Gouret and J. Thomas, *J. Pharmacol.* (Paris), 1973, **4**, 401.
12. G. Raynaud and C. Gouret, *Chim. Ther.*, 1973, **3**, 328.
13. C.K. Fair, 'MolEN, an alternative intelligent system for crystal structure analysis,' Enraf-Nonius, Delft, The Netherlands, 1990.
14. 'International Tables for X-Ray Crystallography,' Vol. 4, Kynoch Press, Birmingham, England, 1974.
15. P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq, and M.M. Woolfson, 'MULTAN 11/82, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data,' Universities of York, England and Louvain, Belgium, 1982.
16. G.H. Stout and L.H. Jensen, 'X-ray Structure Determination : a practical Guide,' Macmillan, New-York, 1968, p. 412.

Received, 4th November, 1997