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]*

[a]Laboratoire de Chimie Thérapeutique; [b]Laboratoire de Chimie Physique et Minérale; [c]Laboratoire de Pharmacologie, Groupe de Recherche en Pharmacochimie, UFR de Pharmacie, 28 Place Henri Dunant, BP 38, 63001 Clermont-Ferrand Cedex, France ; [d]Laboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques, Université François Rabelais, Avenue Monge, 37200 Tours, France

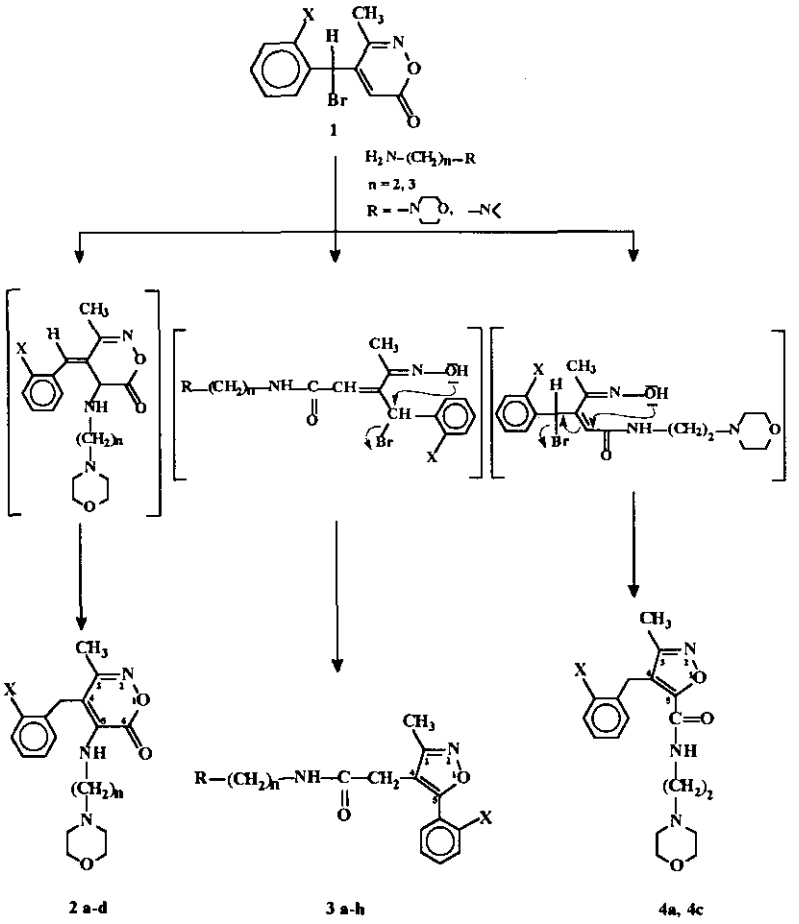
Abstract - Reaction of 4-bromobenzyl-6*H*-1,2-oxazin-6-ones (**1**) with aminoalkylamines furnished a mixture of 5-aminoalkylamino-6*H*-1,2-oxazin-6-ones (**2**), 4-(aminoalkylaminocarbonylmethyl)isoxazoles (**3**) and 5-(Aminoalkylaminocarbonyl)-isoxazoles (**4**) which were separated by column chromatography. Structure of all derivatives was determined by ^{1}H- and ^{13}C-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-6*H*-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 occured 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	$C_{18}H_{23}N_3O_3$	65.63 (65.42	7.04 7.18	12.76 12.49)	
2b	H	3	8	71-83	$C_{19}H_{25}N_3O_3$	66.44 (66.72	7.34 7.28	12.24 12.15)	
2c	Cl	2	5	yellow oil	$C_{18}H_{22}N_3O_3Cl$	59.42 (59.21	6.10 6.33	11.55 11.63	9.74 9.81)
2d	Cl	3	16	yellow oil	$C_{19}H_{24}N_3O_3Cl$	60.39 (60.38	6.40 6.72	11.12 11.14	9.38 9.20)

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

Compd	IR (cm^{-1}, KBr) ν N-H	ν C=O	^{1}H-NMR ($CDCl_3$, δ, ppm)
2a	3630-3240	1700	2.16 (3H, s, CH_3), 2.37 (4H, t, J = 4.5 Hz, 2 CH_2 morph.), 2.48 (2H, t, J = 5.9 Hz, CH_2), 3.63 (2H, dt, J = 5.9 and 4.8 Hz, CH_2), 3.83 (4H, t, J = 4.5 Hz, 2 CH_2 morph.), 3.92 (2H, s, CH_2-C_6H_5), 6.02 (1H, t, J = 4.7 Hz, N-H), 7.15-7.39 (5H, m, C_6H_5)
2b	3660-3160	1695	1.68 (2H, quint, 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, J = 6.2 Hz, CH_2), 3.68 (4H, t, J = 4.6 Hz, 2 CH_2 morph.), 3.93 (2H, s, CH_2-C_6H_5), 6.77 (1H, br s, N-H), 7.12-7.33 (5H, m, C_6H_5)
2c	3620-3120	1695	2.11 (3H, s, CH_3), 2.33 (4H, t, J = 4.5 Hz, 2 CH_2 morph.), 2.44 (2H, t, J = 5.8 Hz, CH_2), 3.48 (2H, dt, J = 5.8 and 5.0 Hz, CH_2), 3.58 (4H, t, J = 4.5 Hz, 2 CH_2 morph.), 3.89 (2H, s, CH_2-C_6H_4), 6.02 (1H, br s, N-H), 6.93-7.47 (4H, m, C_6H_4)
2d	3700-3100	1695	1.68 (2H, quint, 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, J = 6.2 Hz, CH_2), 3.71 (4H, t, J = 4.7 Hz, 2 CH_2 morph.), 3.94 (2H, s, CH_2-C_6H_4), 6.90 (1H, br s, N-H), 6.98-7.45 (4H, m, C_6H_4)

Table 3. ^{13}C-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**).

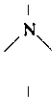
Compd	X	R	n	Yield (%)	mp (°C)	Formula	Analysis % Calcd (Found) C	H	N	Cl
3a	H		2	33	119-123	$C_{18}H_{23}N_3O_3$	65.63 (65.45	7.04 6.92	12.76 13.01)	
3b	H		3	58	150-162	$C_{19}H_{25}N_3O_3$	66.44 (66.75	7.34 7.16	12.24 12.16)	
3c	Cl		2	22	93-101	$C_{18}H_{22}N_3O_3Cl$	59.42 (59.25	6.10 6.37	11.55 11.72	9.74 9.82)
3d	Cl		3	39	brown oil	$C_{19}H_{24}N_3O_3Cl$	60.39 (60.32	6.40 6.71	11.12 11.23	9.38 9.02)
3e	H		2	28	111-115	$C_{16}H_{21}N_3O_2$	66.87 (66.47	7.37 7.24	14.63 14.85)	
3f	H		3	24	102-105	$C_{17}H_{23}N_3O_2$	67.74 (68.01	7.69 7.48	13.95 14.05)	
3g	Cl		2	19	yellow oil	$C_{16}H_{20}N_3O_2Cl$	59.71 (59.57	6.26 6.21	13.06 13.31	11.02 10.69)
3h	Cl		3	31	yellow oil	$C_{17}H_{22}N_3O_2Cl$	60.80 (60.51	6.60 6.75	12.52 12.84	10.56 10.37)

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

Compd	IR (cm^{-1}, KBr) ν N-H	ν C=O	^{1}H-NMR ($CDCl_3$, δ, ppm)
3a	3660-3140	1645	2.32-2.33 (7H, m, CH_3+2 CH_2 morph.), 2.41 (2H, t, J = 5.9 Hz, CH_2), 3.34 (2H, dt, J = 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_6H_5)
3b	3660-3160	1635	1.71 (2H, quint, J = 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, J = 6.6 and 5.1 Hz, CH_2), 3.54 (2H, s, CH_2-C=O), 3.65 (4H, t, J = 4.6 Hz, 2 CH_2 morph.), 6.80 (1H, t, J = 4.8 Hz, N-H), 7.49-7.71 (5H, m, C_6H_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, J = 4.5 Hz, 2 CH_2 morph.), 6.56 (1H, br s, N-H), 7.36-7.52 (4H, m, C_6H_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, J = 4.5 Hz, 2 CH_2 morph.), 7.17 (1H, br s, N-H), 7.31-7.43 (4H, m, C_6H_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, J = 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_6H_5)
3f	3360-3140	1645	1.54 (2H, quint, J = 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, J = 5.6 and 4.7 Hz, CH_2), 3.50 (2H, s, CH_2-C=O), 7.45-7.69 (5H, m, C_6H_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_6H_4)
3h	3620-3120	1650	1.33 (2H, quint, J = 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_6H_4), 7.64 (1H, t, J = 4.9 Hz, N-H)

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

Compd	CH_3	$N(CH_3)_2$	$\underline{C}H_2$-C=O	$(CH_2)_n$	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	$C_{18}H_{23}N_3O_3$	65.63 (65.51	7.04 7.19	12.76 13.01)	
4c	Cl	2	10	96-108	$C_{18}H_{22}N_3O_3Cl$	59.42 (59.05	6.10 6.47	11.55 11.43	9.74 9.79)

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

Compd	IR (cm^{-1}, KBr)		^{1}H-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, $C\underline{H}_2$-C_6H_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, $C\underline{H}_2$-C_6H_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.	$(CH_2)_n$	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 ^{1}H-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 ^{1}H-^{13}C long-range correlations determined by a selective INEPT experience (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 ^{1}H-^{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 C$\underline{H_2}$-C(4) at 3.32 ppm. But no correlation was found between aromatic carbons and C$\underline{H_2}$-C(4). On the contrary, INEPT spectrum of **4c** showed a long-range correlation between aromatic carbons and C$\underline{H_2}$-C(4) at 4.31 ppm, but no correlation between carbonyl group at 157.2 ppm and C$\underline{H_2}$-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 program[7] are given in Figure 1.

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

Irradiated protons	Compds 2	Compds 3	Compds 4
CH$_3$	C=N, C(4)	C=N, C(4)	C=N, C(4)
C$\underline{H_2}$-C(4)	C(4), Ar, C(5), C=N	C=O, C(4), C=N, C(5)	C(4), Ar, C(5), C=N
C$\underline{H_3}$-NH	C(5)	C=O	C=O
NH	C(4), C=O	C=O	C=O
Ar ortho	$\underline{C}$H$_2$-C(4), Ar	C(5), Ar	$\underline{C}$H$_2$-C(4), Ar

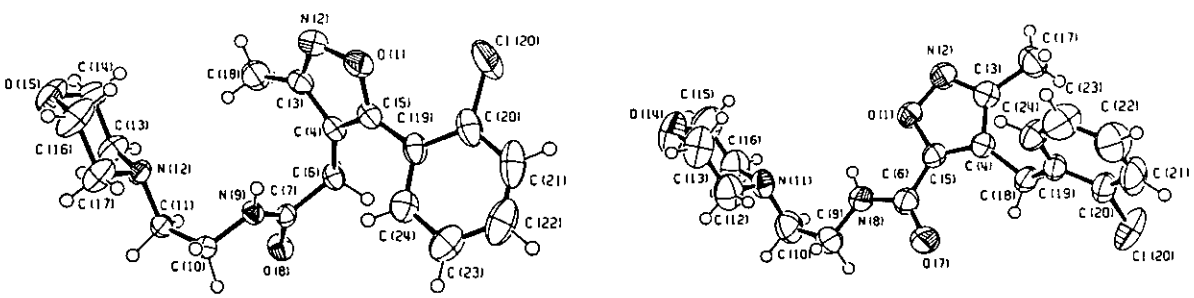


Figure 1. ORTEP drawings of **3c** (left) and **4c** (right) showing 50 % probability displacement ellipsoïds

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 described[1] 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 test[10] 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 $CDCl_3$ 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 (35-70μm, 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*-morpholino-ethylaminocarbonyl)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 $NaHCO_3$ (30 mL), and extracted with chloroform (3 × 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	$C_{18}H_{22}N_3O_3Cl$	$C_{18}H_{22}N_3O_3Cl$
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	$Pna2_1$	$P2_1/c$
a (Å)	10.211(2)	15.738(5)
b (Å)	22.346(3)	7.275(1)
c (Å)	8.032(2)	17.489(2)
β (°)		111.59(2)
V (Å^3)	1832.7(9)	1861.9
Z	4	4
D_{calc} (g.cm^{-3})	1.32	1.30
F (000)	768	768
Data collection		
θ limits (°)	$1 \le \theta \le 35$	$1 \le \theta \le 30$
Nber. of measured reflections	4249	4490
Nber. of independant reflections	4249	4490
Nber. of observed reflections with $I \ge 1.5\ \sigma(I)$	2666	2130
Standard reflections	3	3
Frequency (s)	3600	3600
Intensity decay	2 %	2 %
Data collected	$0 \le h \le 16$	$-25 \le h \le 25$
	$0 \le k \le 36$	$0 \le k \le 11$
	$0 \le l \le 12$	$0 \le l \le 28$
Refinement on F		
Final R	0.045	0.053
ωR	0.039	0.051
S	2.04	1.69
Nber. of reflections	2665	2118
Nber. of parameters	314	315
ω	$1/\sigma^2(F)$	$1/\sigma^2(F)$
$(\Delta/\sigma)_{max}$	0.01	0.01
Max. and min. electron density	0.24	0.20
in final Fourier difference map (e Å^{-3})	- 0.28	- 0.19
Extinction coefficient g[a]	5.86×10^{-7}	1.79×10^{-7}

[a] $F_c = |F_o|\ (1 + g\ I_c)^{-1/6}$

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 (λ = 0.71069 Å). Crystals data are listed in Table 11. Lattice parameters were obtained by least-squares refinement of 25 reflections with $8 < \theta < 20°$. The intensity data were collected in an θ - 2θ 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. Albuisson, 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. Giannoti, 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