SYNTHESIS AND CONFIGURATIONAL STUDY OF 2-ARYLMORPHOLINES

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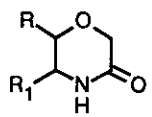
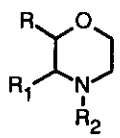
Abstract - The synthesis of various 2-(2,3-dihydro-3-methyl-2-oxobenz[*d*]oxazol-6-yl)morpholines is reported. It has been demonstrated that 2-hydroxymorpholines or β-hydroxyethylaminomethyl ketones are formed as intermediates as assessed by ir, uv, ^1H and ^{13}C nmr analyses. The configuration of the title compounds was also established and corresponds to an equatorial orientation of the aromatic substituent which is considered as essential for an adrenergic activity.

The 2-arylmorpholines exhibit pharmacological properties such as muscular relaxation (Flumetramide[1]), antidepression (Fenmetramide,[1] Viloxazine,[2] Oxaflozane[3a,b]), vasoconstriction (Abiadin[3d]), analgesia (Flumexadol[3e]) or anorexia (Phendimetrazine[4]).





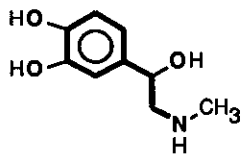
R	R_1	
$C_6H_4CF_3$ (p)	H	Flumetramide
C_6H_5	CH_3	Fenmetramide

R	R_1	R_2	
$C_6H_5CH_2O$	C_2H_5O	H	Viloxazine
$C_6H_4CF_3$ (m)	H	$CH(CH_3)_2$	Oxaflozane
$C_6H_3(OH)_2$ (m, p)	H	H	Abiadin
C_6H_5	CH_3	CH_3	Phendimetrazine
$C_6H_4CF_3$ (m)	H	H	Flumexadol

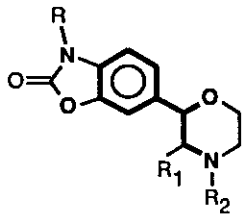
They can be considered as semirigid analogues of arylethanolamines; the levels of their adrenergic activity[5] depend upon parameters such as steric or electronic effects arising from additional substituents necessary to maintain the rigid conformation or from the orientation of the unshared electron pair of the nitrogen atom.[6] For instance, it has been shown

that 2-(4-nitrophenyl)morpholines possess a weak β adrenergic activity[7] and 2-(2,4-dimethoxyphenyl)morpholines exhibit only α-blocking activity in contrast to their opened counterparts.[8]

The study of 6-(2-hydroxyethyl)benz[*d*]oxazol-2(3*H*)-one derivatives with adrenergic activities[9] led us to the design of hybrid molecules (**6a-e**) where the skeleton of norepinephrine is modified on the basis of steric and bioisosteric considerations.[10] So, (i) the OH and NH groups are included in a morpholine heterocycle, (ii) the benz[*d*]oxazol-2(3*H*)one heterocycle is condensed with the phenyl group, (iii) the carbon atom at α-position to the amino function is possibly substituted in order to modulate both the α and β adrenergic activities,[11] (iv) the morpholinic nitrogen can be substituted by alkyl groups.



Norepinephrine



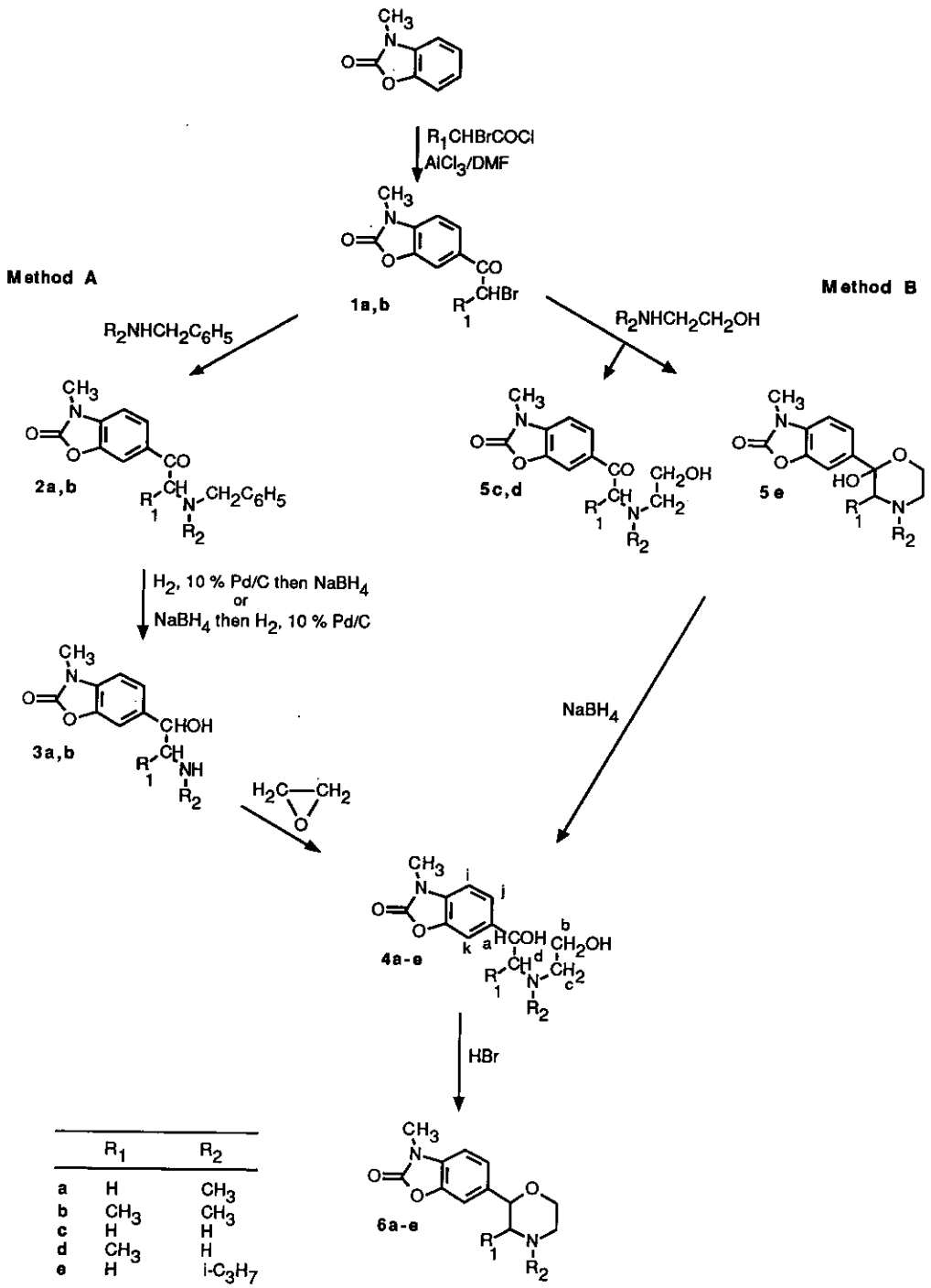
2-(2,3-Dihydro-2-oxobenz[*d*]oxazol-6-yl)morpholines (**6a-e**)

RESULTS AND DISCUSSION

The bis(2-hydroxyethyl)amines (**4**), precursors of the 2-arylmorpholines (**6**), were prepared by two convenient synthetic routes (methods A and B, Scheme) chosen according to the accessibility of the starting materials. The 6-bromoacyl-3-methylbenz[*d*]oxazol-2(3*H*)-ones (**1**) were unequivocally prepared in high yields by acylation of 3-methylbenz[*d*]oxazol-2(3*H*)-one with the appropriate aliphatic acid chlorides, using the aluminum chloride-dimethylformamide mixture as catalyst.[12] This method was found more general and efficient than the classical one[13] which involved polyphosphoric acid as catalyst and solvent. This regioselective acylation occurred at C(6), as was ascertained by X-ray diffraction on 6-benzoylbenz[*d*]oxazol-2(3*H*)-one.[14]

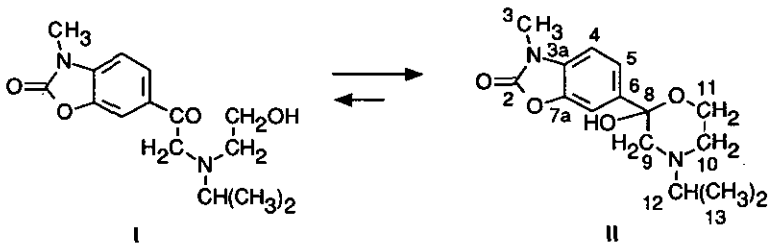
In method A, the bromoacyl derivatives (**1a,b**) were condensed with the appropriate benzylamine to afford the corresponding α-amino ketones (**2a,b**). Reduction with sodium borohydride (coupled with catalytic debenzylation) provided the 2-amino alcohols (**3a,b**) as previously described.[9c] The separation of stereoisomers was accomplished by selective crystallization in the case of **3b**. The predominant derivative (80% yield) possesses the threo configuration as assessed with ^{1}H nmr by the vicinal protons coupling constant (J = 10 Hz). Use of ethylene oxide afforded the bis(2-hydroxyethyl)amines (**4a,b**). The final dehydration into 2-arylmorpholines (**6a,b**) was achieved by aqueous hydrobromic acid catalysis.

In an alternative approach (method B), the α-bromo ketones (**1a,b**) were reacted with the appropriate alkylethanolamines to give the β-amino ketones (**5c,d**) whose reduction with sodium borohydride led to the amino diols (**4c,d**).The vicinal coupling constant evidenced an erythro configuration for **4d**. Dehydrative cyclization was accomplished as previously mentioned for **6a,b** to afford the 2-arylmorpholines (**6c,d**). All hydroxy ketones were characterised by their ^{1}H nmr and ir spectra.



	R_1	R_2
a	H	CH_3
b	CH_3	CH_3
c	H	H
d	CH_3	H
e	H	i-C_3H_7

Scheme



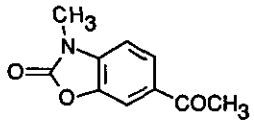
I II

5e

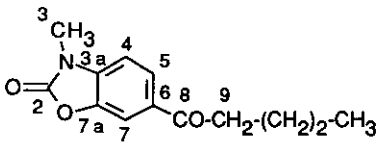
However, it was noted that **5e** presents an hydroxyl absorption around 3360 cm^{-1} and lacks the carbonyl band at 1680 cm^{-1}. Such a characteristic is in favour[15] of a hemiketal form **II** resulting from the cyclization of the corresponding hydroxy ketone (**I**). Indeed, if the synthesis of 2-hydroxymorpholines can be unequivocally directed,[16] it is also described[17] that this heterocycle may result from the chain-ring tautomerism with the β-hydroxyethylaminomethyl ketones. Such a cyclization is enhanced by different factors inducing an adequate conformation, namely a bulky alkyl group on the nitrogen[18,19] or on the vicinal carbon, a decrease of the strain produced by the close proximity of the OH and CO functions or to the protonation of the amine.[15,20] In the case of **5e**, the bulky isopropylamino substituent on the nitrogen and the predominent donor effect of the nitrogen of the benz[*d*]oxazole entity (as attested by its preferential electrophilic substitution on C(6)) are determinent to induce the conformation leading to the cyclization.

This hypothesis is supported by the fact that the 6-acyl-3-methylbenz[*d*]oxazol-2(3*H*)-one uv absorbance at 296 nm (**5c**) undergoes a hypsochromic shift (13 nm) and a pronounced decrease of ε_{max} for **5e**, as was also noticed by Griffin[17] in a similar case.

Table I. Uv - visible spectral characteristics (λ_{max}, nm) and ε (λ_{max}) of **7**,[12a] **5c,e** in 50 % aqueous dioxane (v/v)

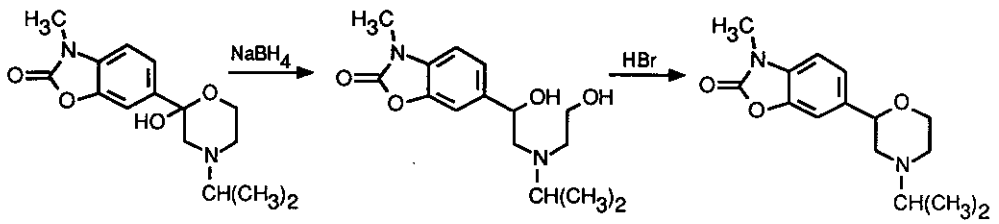
Compd	λ_{max}	ε_{max}
 **7**	273	14 490
	289	14 320
5c	280	11 625
	296	11 610
5e	278	6 265
	283	5 530

A definitive demonstration is given by nmr (Tables II and III) : **5e** showed an OH resonance around 5 ppm (broad signal exchangeable with D_2O),[21] instead of a 3 ppm centered one for a primary alcoholic function; the 94.4 ppm resonance, in the range of values currently observed[22] for the anomeric carbon of carbohydrates, replaces the 198.3 ppm one characterisitic of the keto carbon of **8**.[23]



8

It appears that a CH_3 on the nitrogen or on C_α is not too bulky to induce a spontaneous cyclization of the keto aminoalcohols (**5c,d**) which occurs in counterpart with a isopropyl *N*-substituent as for **5e**. The configuration at the asymetric carbon of **5e** cannot be deduced from the sequence **5e** ——> **6e** which involves the reductive cleavage ($NaBH_4$)[24] followed by the closure step (HBr medium) implying a secondary carbocation.



5e **4e** **6e**

Table II. Physical data of compounds **4a-e,5c-e**

Compd[a]	Yield %	mp (°C) (Recryst. solvent)	Anal. Calcd (Found) C	H	N	^{1}H nmr data (ppm)
4a	70	70-71 (Cyclohexane)	58.63 (58.55)	6.81 (6.85)	10.52 (10.40)	[b] 2.30 (s, 3H, CH_3) ; 2.70 (m, 4H, H_c, H_d) ; 3.38 (s, 3H, CH_3N) ; 3.75 (t, 2H, H_b, J_{Hb-Hc} = 5.25 Hz) ; 3.85 (s, 2H, OH^c) ; 4.75 (t, 1H, H_a, J_{Ha-Hd} = 6 Hz) ; 7.28 (m, 2H, H_i, H_j) ; 7.47 (s, 1H, H_k)
4b[d]	84	108-110 (Toluene)	59.77 (59.98)	7.52 (7.19)	9.95 (9.99)	[b] 0.73 (d, 3H, CH_3, J_{CH3-Hd} = 7 Hz) ; 2.30 (s, 3H, CH_3) ; 2.60 (m, 3H, H_c, H_d) ; 3.35 (s, 3H, CH_3) ; 3.70 (t, 2H, H_b) ; 3.86 (s, 2H, OH^c) ; 4.40 (c, 1H, H_a, J_{Ha-Hd} = 10 Hz) ; 6.86 (d, 1H, H_i, J_{i-j} = 7.5 Hz) ; 7.06 - 7.22 (m, 2H, H_j, H_k)
4c[e]	75	184-186 (Ethanol)	49.91 (49.61)	5.93 (5.80)	9.70 (9.59)	[f] 2.75 (m, 4H, H_c, H_d) ; 3.45 (s, 3H, CH_3N) ; 3.57 (t, 2H, H_b, J_{Hb-Hc} = 5.25 Hz) ; 4.00 - 4.40 (m, 3H, OH^c, NH^c) ; 4.82 (t, 1H, H_a, J_{Ha-Hd} = 6 Hz) ; 7.30 (m, 2H, H_i, H_j) ; 7.50 (s, 1H, H_k)
4d[g]	70	145-146 (Toluene)	58.63 (58.38)	6.81 (6.81)	10.52 (10.35)	[f] 0.85 (d, 3H, CH_3, J_{CH3-Hd} = 6.75 Hz) ; 2.55 - 2.90 (m, 3H, H_c, H_d) ; 3.22 - 3.82 (m, 8H, CH_3N, H_b, OH^c, NH^c) ; 4.75 (d, 1H, H_a, J_{Ha-Hd} = 5.25 Hz) ; 7.37 (m, 2H, H_i, H_j) ; 7.47 (s, 1H, H_k)

Table II. (continued)

4e	80	90-91 (Cyclohexane)	61.20 (61.18)	7.53 (7.60)	9.15 (9.22)	[b] 1.07 (d, 6H, CH_3, $J_{CH_3\text{-}CH}$ = 6.75 Hz) ; 2.75 (m, 4H, H_c, H_d) ; 3.02 (q, 1H, CH, $J_{CH\text{-}CH_3}$ = 6.75 Hz) ; 3.45 (s, 3H, CH_3N) ; 3.72 (t, 2H, H_b, $J_{H_b\text{-}H_c}$ = 6 Hz) ; 3.81 (s, 2H, OH^c) ; 4.80 (m, 1H, H_a) ; 7.07 (d, 1H, H_i, $J_{i\text{-}j}$ = 9 Hz) ; 7.25 - 7.45 (m, 2H, H_j, H_k)
5c	60	137-138 (Ethanol 95)	57.59 (57.22)	5.64 (5.57)	11.19 (11.18)	[f] 2.82 (m, 2H, H_c) ; 3.42 (s, 3H, CH_3N) ; 3.55 - 3.92 (m, 4H, H_b, OH^c, NH^c) ; 4.25 (s, 2H, H_d) ; 7.75 (d, 1H, H_i, $J_{i\text{-}j}$ = 7.5 Hz) ; 8.17 (m, 2H, H_j, H_k)
5d	80	145-147 (Ethanol 95)	59.08 (59.03)	6.10 (6.07)	10.60 (10.44)	[f] 1.25 (d, 3H, $J_{CH_3\text{-}H_d}$ = 6.75 Hz) ; 2.67 (m, 2H, H_c) ; 2.90 - 3.00 (m, 1H, OH^c) ; 3.52 (m, 5H, CH_3N, H_b) ; 3.95 - 4.00 (m, 1H, NH^c) ; 4.55 (q, 1H, H_d, $J_{CH_3\text{-}H_d}$ = 6.75 Hz) ; 7.57 (d, 1H, H_i, $J_{i\text{-}j}$ = 7.5 Hz) ; 8.15 - 8.30 (m, 2H, H_j, H_k)
5e	55	110-111 (Cyclohexane)	61.62 (61.84)	6.89 (7.03)	9.58 (9.47)	[b] 0.98 (d, 6H, CH_3, $J_{CH_3\text{-}CH}$ = 6.75 Hz) ; 2.70 (m, 5H, H_c, H_d, NH^c) ; 3.35 (s, 3H, CH_3N) ; 4.10 (m, 2H, H_b) ; 4.80 - 5.10 (m, 1H, OH^c) ; 6.82 (d, 1H, H_i, $J_{i\text{-}j}$ = 8.25 Hz) ; 7.50 - 7.63 (m, 2H, H_j, H_k)

[a] See **4a-e** (Scheme) for designation of atoms. [b] Base, solvent $CDCl_3$. [c] Exchangeable with D_2O. [d] Threo isomer. [e] Hydrochloride. [f] Base, solvent DMSO-d_6. [g] Erythro isomer.

Table III. ^{13}C nmr data (400 MHz) of compounds **5e,8,6a,e** in $CDCl_3$

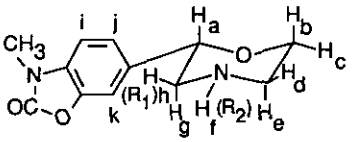
Compd[a]	2	3	3a	4	5	6	7	7a	8	9	10	11	12	13
5e	155.0	28.2	131.6	108.0	121.5	137.3	107.3	142.4	94.4[b]	60.6	54.7	59.7	48.2	17.8 ; 18.1
8[23]	154.4	28.2	132.0	107.3	124.9	135.4	109.2	142.3	198.3	38.0				
6a									78.9	63.5	55.8	68.2		
6e	154.6	27.9	131.0	107.8	121.6	135.7	107.4	142.4	77.8	56.5	54.6	67.1	48.1	18.0 ; 18.3

[a] See formulae **5e,8** in text for atoms numbering. [b] C(6)-C(8) axial bond.

However, the fact that the C(8) of morpholine cycle experiences a marked shielding (78.9 vs. 94.4 ppm) when comparing **6a** with **5e** is indicative of the axial position of the phenyl group.[25] On an other hand, the coupling constant of 9 Hz between H_a and the vicinal proton H_g is in accordance[26] with the equatorial position occupied both by the aromatic and the R_1 substituents for the 2-arylmorpholines (**6a-e**)[27] (Table IV). This configuration inversion between **5e** and **6e** may be explained if we suppose that the cyclization step **4e** ——> **6e**, effected with strong acid, proceeds preferentially via a

planar benzyl carbonium ion, as illustrated by the respective stereochemistry of **4d** (erythro) and **6d** (equatorial aryl and methyl substituents), and favors the thermodynamically more stable conformers.

Table IV. Physical data of compounds **6a-e**



Compd[a]	Yield %	mp (°C) (Recryst. solvent)	Anal. Calcd (Found) C	H	N	^{1}H nmr data (ppm)
6a[b]	70	> 260 (Ethanol)	62.89 (62.49)	6.49 (6.65)	11.28 (11.14)	[c] 1.93 - 2.20 (m, 2H, H_d, H_e) ; 2.39 (s, 3H, CH_3) ; 2.73 - 3.03 (m, 2H, H_g, H_h) ; 3.46 (s, 3H, CH_3N) ; 3.75 - 4.24 (m, 2H, H_b, H_c) ; 4.66 (dd, 1H, H_a, J_{Ha-Hg} = 9 Hz, J_{Ha-Hh} = 3 Hz) ; 7.04 (d, 1H, H_i, J_{i-j} = 7 Hz) ; 7.30 (m, 2H, H_j, H_k)
6b	77	161-163 (Ethanol)	50.43 (50.43)	5.92 (6.07)	7.84 (7.72)	[c] 0.84 (d, 3H, CH_3, J_{CH3-Hg} = 7 Hz) ; 2.08 - 2.22 (m, 1H, H_g) ; 2.33 (s, 3H, CH_3) ; 2.33 - 2.82 (m, 2H, H_d, H_e) ; 3.35 (s, 3H, CH_3N) ; 3.82 - 3.93 (m, 2H, H_b, H_c) ; 4.04 (d, 1H, H_a, J_{Ha-Hg} = 9 Hz) ; 6.82 (d, 1H, H_i, J_{i-j} = 8 Hz) ; 7.08 (m, 2H, H_j, H_k)
6c[b]	75	> 260 (Ethanol)	45.72 (45.75)	4.79 (4.83)	8.88 (8.87)	[c] 2.26 (s, 1H, NH[d]) ; 2.55 - 3.11 (m, 4H, H_d, H_e, H_g, H_h) ; 3.35 (s, 3H, CH_3N) ; 3.82 (m, 2H, H_b, H_c) ; 4.44 (dd, 1H, H_a, J_{Ha-Hg} = 9 Hz, J_{Ha-Hh} = 3 Hz) ; 6.88 (d, 1H, H_i, J_{i-j} = 7 Hz) ; 7.15 (m, 2H, H_j, H_k)
6d[b]	70	>260 (Ethanol)	47.43 (47.14)	5.21 (5.26)	8.51 (8.45)	[e] 1.02 (d, 3H, CH_3, J_{CH3-Hg} = 7 Hz) ; 2.96 - 3.77 (m, 6H, CH_3N, H_d, H_e, H_g) ; 3.93 - 4.17 (m, 2H, H_b, H_c) ; 4.45 (d, 1H, H_a, J_{Ha-Hg} = 10 Hz) ; 7.24 (m, 2H, H_i, H_j) ; 7.40 (s, 1H, H_k) ; 9.22 - 9.60 (m, 2H, NH_2[d])
6e[b]	75	>260 (Water)	50.43 (50.43)	5.92 (6.07)	7.84 (7.72)	[c] 1.12 (d, 6H, CH_3, J_{CH3-Hg} = 7.5 Hz) ; 2.05 - 3.10 (m, 5H, CH, H_d, H_e, H_g, H_h) ; 3.47 (s, 3H, CH_3N) ; 3.72 - 4.00 (m, 2H, H_b, H_c) ; 4.75 (dd, 1H, H_a, J_{Ha-Hg} =10.5 Hz, J_{Ha-Hh} = 3 Hz) ; 7.08 (d, 1H, H_i, J_{i-j} = 9 Hz) ; 7.42 (m, 2H, H_j, H_k)

[a] Preferential equatorial substitution. [b] Hydrobromide. [c] Base, solvent $CDCl_3$. [d] Exchangeable with D_2O. [e] Hydrobromide, solvent DMSO-d_6.

EXPERIMENTAL SECTION

Melting points were taken on a Tottoli Büchi 510 apparatus and are uncorrected. The ir spectra were recorded with a Perkin Elmer 1310 spectrophotometer using potassium bromide pellets. The ^{1}H and ^{13}C nmr spectra were recorded on Bruker WP 80 SY and Bruker 400 spectrometers. Chemical shifts are reported in ppm from tetramethylsilane as an internal standard and are given in δ units.

6-(2-Hydroxyethylaminoacetyl)-3-methylbenz[*d*]oxazol-2(3*H*)-one (5c).

A mixture of **1a**[12b] (6.75 g, 25 mmol), acetonitrile (10 ml) and ethanolamine (3.25 g, 50 mmol) was stirred for 1 h at room temperature. The precipitate was collected, washed with ether and dissolved in 1N HCl. After filtration, the solution was made basic (pH 9) with 10% aqueous Na_2CO_3 and the resulting precipitate was collected, washed and recrystallized from ethanol 95% to give 3.75 g (60% yield) of **5c**. Ir : 1680, 1770, 3200, 3300. See Table II.

6-[2-(2-Hydroxyethylamino)propionyl]-3-methylbenz[*d*]oxazol-2(3*H*)-one (5d).

1b[12a] (8.52 g, 30 mmol) was dissolved in 90 ml of hot acetonitrile. After cooling, methylamino ethanol (3.66 g, 60 mmol) was added. The mixture was stirred for 15 h at room temperature. The precipitate was collected, washed with ether, dissolved in 1N HCl. After filtration, the solution was made basic (pH 9) with 10% aqueous Na_2CO_3. The resulting precipitate was collected, washed and recrystallized from ethanol 95% to give **5d** (6.4 g, 80 % yield). Ir : 1670, 1470, 3150, 3300. See Table II.

2-(2,3-Dihydro-3-methyl-2-oxobenz[*d*]oxazol-6-yl)-2-hydroxy-4-isopropylmorpholine (5e).

1a[12b] (2.7 g, 10 mmol) was dissolved in 60 ml acetonitrile and isopropylamino ethanol (2.06 g, 20 mmol) was added. The mixture was stirred for 15 h at room temperature. After evaporation of acetonitrile under vacuum, the residue was treated with 1N HCl, the mixture was filtered and the filtrate was made basic (pH 9) with 10% aqueous Na_2CO_3. The resulting precipitate was collected, washed with water and recrystallized from cyclohexane to give **5e** (1.6 g, 55% yield). Ir : 3360, 1770. See Table II.

6-[1-Hydroxy-2-(2-hydroxyethylamino)ethyl]-3-methylbenz[*d*]oxazol-2(3*H*)-ones.

General procedure for the preparation of (4a,b).

The amino alcohol (**3a** or **b**)[9c] (10 mmol) was dissolved in methanol (100 ml). Ethylene oxide (20 mmol) was bubbled in the solution. The mixture was stirred 8 h at room temperature and then evaporated under vacuum. The residue was recrystallized in the appropriate solvent or transformed into the corresponding base by neutralization (Na_2CO_3) of the aqueous solution. See Table II.

General procedure for the preparation of (4c-e).

To a suspension of compounds **5c,d** or **e** (10 mmol) in methanol (100 ml) was added, under stirring at room temperature, sodium borohydride (0.76 g, 20 mmol). The mixture was stirred 4 h at room temperature and then acidified with 6N HCl and evaporated under vacuum. The residue was recrystallized from the appropriate solvent or transformed into the corresponding base as mentioned for **4a,b**. See Table II.

General procedure for the preparation of 2-(2,3-Dihydro-3-methyl-2-oxobenz[*d*]oxazol-6-yl)morpholines (6a-e).

A mixture of the diols (**4a-e**) (10 mmol) and 10 ml of 48 % hydrobromic acid was refluxed for 1 h. The solid which precipitated *in situ* was collected after complete evaporation of the hydrobromic solution, washed with water and recrystallized or transformed into the corresponding base as precedently described. Ir : 1770, 1050-1150, 2900-3050. See Table IV.

REFERENCES AND NOTES

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