Synthesis of New [[(3-Substituted-5-isoxazolyl)-alkyliden]iminooxy]aminopropanol Derivatives

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The preparation of new [[(3-substituted-5-isoxazolyl)alkyliden]iminooxy]aminopropanol compounds is reported starting from the corresponding 1-isoxazolylalkanones. The ^{1}H- and ^{13}C-nmr studies, carried out to establish the *Z*- and *E*-configuration of new derivatives, are also described.

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In a previous paper [1] we described the synthesis and the pharmacological evaluation of a series of β_2-adrenergic isoxazoles. Recently [2] we extended this study preparing a number of isoxazole aminoalcohols bearing substituents different from the previously reported [1] 3-halo and 3-alkoxy groups. In the past few years Lecrerc and coworkers reported the synthesis of oxime derivatives [3,4,5] having a marked β-blocking activity. Their data showed that the intercalation of an iminic function in the side chain of the β-blockers leads, in some cases, to potent and selective β_2-agonists.

In continuing our program of synthesis and utilization of potentially active β-adrenergic isoxazoles, we prepared new aromatic oxymino derivatives **4a-h** which presented the isoxazole nucleus as aromatic moiety.

Scheme 1 illustrates the synthetic approach used for the preparation of alkylaminopropanol derivatives **4a-f**. Known ketones **1a-c** [6,7] were treated with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol at reflux to give already described oxime **2a** [6] and new oximes **2b-c**. Analytical data of derivatives **2b-c** are presented in the experimental and ^{1}H-nmr data of compounds **2a-c** are shown in Table 1.

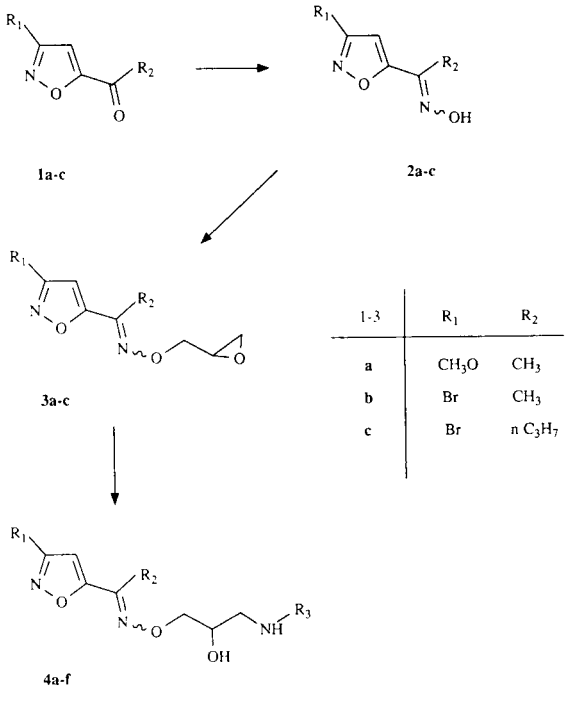
It was reported [6] that the action of hydroxylamine on ketone **1a** under basic conditions gave a mixture of *Z*- and **E**-oxime derivatives in a ratio of *ca.* 20:80 after crystallization from water. The same authors confirmed in a following paper [8] the configuration of *Z*- and *E*-isomers of ox-

Table 1

^{1}H-NMR Data of Compounds **2a-c** and **4a-h**

Compound	δ (ppm), DMSO-d_6
2a	12.10 and 12.00 (s, 0.02 and 0.98H), 7.21 and 6.53 (s, 0.02 and 0.98H), 3.95 and 3.90 (s, 0.06 and 2.94H), 2.16 and 2.08 (s, 0.06 and 2.94H)
2b	12.34 and 12.23 (s, 0.01 and 0.99H), 7.40 and 7.13 (s, 0.01 and 0.99H), 2.22 and 2.12 (s, 0.03 and 0.97H)
2c	12.39 and 12.19 (s, 0.26 and 0.74H), 7.40 and 7.15 (s, 0.26 and 0.74H), 2.60 (m, 2H), 1.54 (m, 2H), 0.93 and 0.89 (t, 0.78 and 2.22H)
4a	9.09 (s broad, 1H), 8.73 (s broad, 1H), 6.97 and 6.69 (s, 0.18 and 0.82H), 5.87 and 5.81 (d, 0.18 and 0.82H), 4.18 (m, 3H), 3.95 and 3.91 (s, 0.54 and 2.46H), 3.31 (septet, 1H), 2.94 (m, 2H), 2.19 and 2.16 (s, 0.54 and 2.46H), 1.26 and 1.25 (d, 2.46 and 0.54H), 1.24 and 1.23 (d, 2.46 and 0.54H)
4b	9.14 (s broad, 1H), 8.60 (s broad, 1H), 6.97 and 6.69 (s, 0.1 and 0.9H), 5.87 and 5.82 (d, 0.1 and 0.9H), 4.19 (m, 3H), 3.95 and 3.91 (s, 0.3 and 2.7H), 2.92 (m, 2H), 2.20 and 2.16 (s, 0.3 and 2.7H), 1.30 and 1.19 (s, 8.1 and 0.9H)
4c	9.00 (s broad, 1H), 8.69 (s broad, 1H), 7.53 and 7.29 (s, 0.14 and 0.86H), 5.87 and 5.82 (d, 0.14 and 0.86H), 4.20 (m, 3H), 3.31 (septet, 1H), 2.96 (m, 2H), 2.26 and 2.20 (s, 0.42 and 2.58H), 1.25 (d, 3H), 1.23 (d, 3H)
4d	9.11 (s broad, 1H), 8.59 (s broad, 1H), 7.54 and 7.29 (s, 0.16 and 0.84H), 5.89 and 5.83 (d, 0.16 and 0.84H), 4.21 (m, 2H), 4.20 (m, 1H), 2.92 (m, 2H), 2.26 and 2.20 (s, 0.48 and 2.52H), 1.30 (s, 9H)
4e	10.14 (s, 1H), 7.83 (m, 2H), 7.60 (m, 2H), 7.49 and 7.27 (s, 0.14 and 0.86H), 4.17 (d, 2H), 4.00 (m, 1H), 2.97 (septet, 1H), 2.71 (m, 4H), 2.06 (s, 3H), 1.53 (m, 2H), 1.09 (d, 3H), 0.90 and 0.89 (t, 0.42 and 2.58H)
4f	10.11 (s, 1H), 7.83 (m, 2H), 7.60 (m, 2H), 7.50 and 7.27 (s, 0.23 and 0.77H), 4.20 (d, 2H), 4.04 (m, 1H), 2.79 (m, 2H), 2.63 (m, 2H), 2.05 (s, 3H), 1.54 (m, 2H), 1.09 (s, 9H), 0.90 and 0.89 (t, 0.69 and 2.31H)
4g	10.95 (d, 1H), 10.18 (s, 1H), 7.87 (m, 2H), 7.64 (m, 2H), 7.55 (d, 1H), 7.48 and 7.24 (s, 0.09 and 0.91H), 7.33 (dd, 1H), 7.19 (d, 1H), 7.01 (m, 2H), 4.22 (m, 2H), 3.99 (m, 1H), 2.89 (s, 2H), 2.82 (m, 2H), 2.25 and 2.18 (s, 0.27 and 2.73H), 2.07 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H)
4h	10.21 (s, 1H), 7.86 (m, 2H), 7.65 (m, 2H), 7.47 and 7.23 (s, 0.21 and 0.79H), 6.84 (d, 1H), 6.82 (d, 1H), 6.71 (dd, 1H), 4.16 (m, 2H), 3.93 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 2.89-2.59 (m, 6H), 2.24 and 2.17 (s, 0.63 and 2.37H), 2.07 (s, 3H)

Scheme 1



The geometry of *Z*- and *E*-forms of new derivatives **2b-c** was unambiguously established by ^{1}H-nmr spectra (Table 2) according with the data reported for compound **2a** [8]. In fact we verified that the deshielding effect of the oxygen of the oxymino group when it is closed to the isoxazole ring (*Z*-isomerism), causes a down-field shift of the isoxazole proton at 4 position. Sodium salts of derivatives **2a-c** were treated in *N*,*N*-dimethylformamide with epibromohydrin affording intermediates **3a-c** which were directly transformed into desired compounds **4a-f**. The synthesis of aminoalcohols **4a-f** was carried out in refluxing ethanol using a ten fold excess of the appropriate amine. Analytical data of derivatives **4a-f** are illustrated in Table 3, ^{1}H-nmr data of these molecules are reported in Table 1.

Scheme 2 shows the last step of the synthetic approach used for the preparation of compounds **4g-h**.

Crude intermediate **3b** was treated in refluxing ethanol with a stoichiometric amount of 3-(2-amino-2-methylpropyl)indole and 2-(3,4-dimethoxyphenyl)ethylamine respectively. The choice of indolyl *t*-butylamine and phenethylamine as basic moieties was made on the base of interesting literature results [9,10] in the field of β-blocking agents. Analytical data of compounds **4g-h** are presented in the experimental section, ^{1}H-nmr data of these molecules are shown in Table 1.

It is interesting to note that compounds **4a-h** were obtained as a mixture of *Z*- and *E*-isomers after crystallization of their salts. The geometry of the two isomers was established by ^{1}H-nmr spectra (Table 2) compared with ^{1}H-nmr data of the mixture of *Z*- and *E*-forms of oximes **2a-c**. In Table 2 it is also indicated the ratio between *Z*-and *E*-isomers of aminoalcohols **4a-d**. As expected, also starting from practically pure *E*-isomers **2a-b**, a mixture of both possible isomers of compounds **4a-d** and **4g-h** was obtained. This is due to the oximate anion which would exist in solution as an equilibrium mixture of *Z*- and *E*-forms.

In order to complete the nmr study of the geometry of new compounds **4a-h**, we recorded a ^{13}C-nmr spectrum of a representative derivative. The ^{13}C chemical shifts of the two isomers of selected compound **4c** are illustrated in Table 4.

Scheme 2

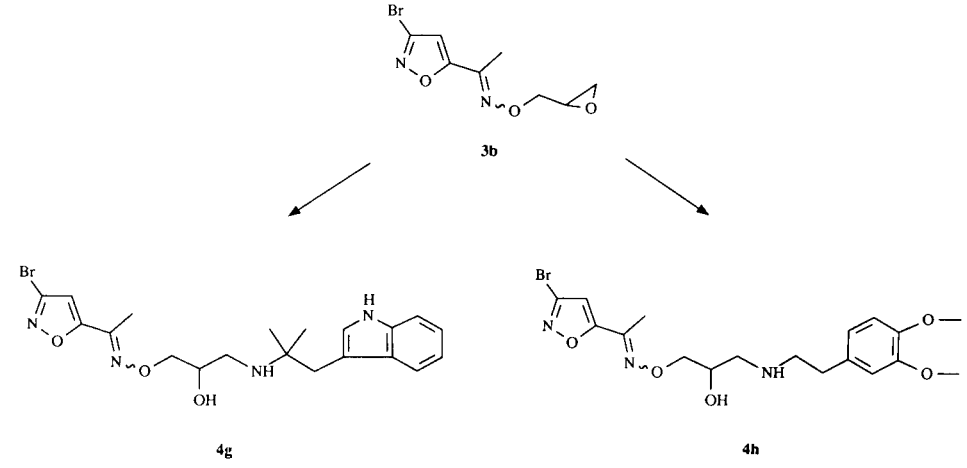


Table 2

^{1}H-NMR Study of *Z*- and *E*-Isomers of Compounds **2a-c** and **4a-h**

Compound	Ratio Z:E	^{1}H-NMR Typical Signals, δ (ppm), DMSO-d$_6$					
		Isoxazole proton		N=C-C*H*$_3$		N=C-(CH$_2$)$_2$-C*H*$_3$	
		Z	*E*	*Z*	*E*	*Z*	*E*
2a	2:98	7.21	6.53	2.16	2.08		
2b	1:99	7.40	7.13	2.22	2.12		
2c	26:74	7.40	7.15			0.93	0.89
4a	18:82	6.97	6.69	2.19	2.16		
4b	10:90	6.97	6.69	2.20	2.16		
4c	14:86	7.53	7.29	2.26	2.20		
4d	16:84	7.54	7.29	2.26	2.20		
4e	14:86	7.49	7.27			0.90	0.89
4f	23:77	7.50	7.27			0.90	0.89
4g	9:91	7.48	7.24	2.25	2.18		
4h	21:79	7.47	7.23	2.24	2.27		

Table 3

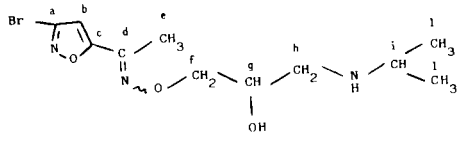
Compounds **4a-f**

Compound	R_1	R_2	R_3	Yield [a], %	Mp, °C [b]	Molecular Formula	Analysis, % (Calcd./Found)		
							C	H	N
4a	CH_3O	CH_3	*i*-C_3H_7	51	167-168	$C_{12}H_{21}N_3O_4$ HCl	46.83	7.20	13.65
							46.89	7.37	13.51
4b	CH_3O	CH_3	*t*-C_4H_9	69	131-132	$C_{13}H_{23}N_3O_4$ HCl	48.52	7.52	13.06
							48.54	7.66	12.97
4c	Br	CH_3	*i*-C_3H_7	42	124-125	$C_{11}H_{18}BrN_3O_3$ HCl	37.04	5.37	11.78
							37.21	5.46	11.78
4d	Br	CH_3	*t*-C_4H_9	51	128-129	$C_{12}H_{20}BrN_3O_3$ HCl	38.88	5.71	11.34
							38.82	5.86	11.28
4e	Br	*n*-C_3H_7	*i*-C_3H_7	53	98-99	$C_{13}H_{22}BrN_3O_3$ H_2O	48.44	6.10	10.27
						$C_9H_9NO_3$ [c]	48.51	6.20	10.26
4f	Br	*n*-C_3H_7	*t*-C_4H_9	61	166-167	$C_{14}H_{24}BrN_3O_3$	51.02	6.14	10.35
						$C_9H_9NO_3$ [c]	51.21	6.22	10.53

[a] Yields calculated from **2a-c**. [b] Crystallization solvent: acetonitrile. [c] 4-Acetaminobenzoic acid.

Table 4

^{13}C-NMR Data of Compound **4c**



	a		b		c		d		e		f	g		h	i	l	l
	Z	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*		*Z*	*E*				
δ (ppm) [a]	141.78	141.33	112.74	107.46	167.38	161.41	140.90	145.65	16.50	12.22	76.70	65.04	65.21	46.78	49.87	18.56	18.14
J_{CH} (cps)			198	193					131	131	146	144	144	142	142	127	127

[a] Measured in DMSO-d$_6$.

New aminoalcohols **4a-h** were tested for their potential β-adrenergic activity; the biological results will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected, boiling point of compound **2c** is also uncorrected. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded with a Varian Gemini 200.

3-Bromo-5-(1-hydroxyiminoethyl)isoxazole **2b**.

A mixture of **1b** (15.1 g, 0.0795 mole), sodium acetate trihydrate (12.44 g, 0.0914 mole) and hydroxylamine hydrochloride (6.35 g, 0.0914 mole) in 50% aqueous ethanol (100 ml) was refluxed for 1 hour. After evaporation of the solvent (50 ml), the resulting solid was collected and crystallized from water to give pure **2b** (14.6 g, 90%, mp 158-159°).

Anal. Calcd. for $C_5H_5BrN_2O_2$: C, 29.29; H, 2.46; N, 13.66. Found: C, 29.41; H, 2.50; N, 13.58.

3-Bromo-5-(1-hydroxyiminobutyl)isoxazole **2c**.

Compound **2c** was similarly prepared as a colorless oil in a yield of 95% (135-140°, 0.6 torr).

Anal. Calcd. for $C_7H_9BrN_2O_2$: C, 36.07; H, 3.89; N, 12.02. Found: C, 36.21; H, 3.83; N, 11.96.

1-[[1-(3-Bromo-5-isoxazoly)-1-ethylidenjiminooxy]-3-isopropylamino-2-propanol Hydrochloride **4c**.

To a stirred solution of **2b** (6.15 g , 0.03 mole) in *N,N*-dimethylformamide (30 ml), 80% sodium hydride suspension in mineral oil (0.9 g, 0.03 mole) was added portionwise at 0°. The obtained yellow solution was dropped at 15° to a stirred solution of epibromohydrin (4.1 g, 0.03 mole) in *N,N*-dimethylformamide (20 ml). After stirring overnight, the mixture was poured into water (200 ml) and extracted twice with chloroform. The organic layer was separated, washed with water, dried and evaporated to give crude **3b** as an oil. To a stirred solution of crude **3b** in ethanol (37 ml) a solution of isopropylamine (25.8 ml, 0.3 mole) in ethanol (60 ml) was added dropwise at 80° and the resulting mixture was refluxed overnight. The solvent was evaporated and the residue was treated with 2*N* hydrochloric acid and chloroform. The aqueous layer was separated and basified with potassium carbonate and the mixture was extracted with ethyl ether. The organic layer was separated, washed with water, dried and treated with a solution of hydrochloric acid in ethyl ether. The resulting solid was collected and crystallized from acetonitrile to give pure **4c** (4.5 g, 42%, mp 124-125°).

Compounds **4a-b** and **4d-f**, listed in Table 3, were similarly prepared.

1-[[1-(3-Bromo-5-isoxazolyl)-1-ethylidenjiminooxy]-3-[2-methyl-3-(3-indolyl)-2-propylamino]-2-propanol 4-Acetaminobenzoate **4g**.

To a stirred solution of crude **3b** (0.03 mole, prepared as described for compound **4c**) in ethanol (78 ml), a solution of 3-(2-amino-2-methylpropyl)indole [9] (5.65 g, 0.03 mole) in ethanol (56 ml) was added dropwise at 80° and the resulting mixture was refluxed overnight. The solvent was evaporated and the residue was treated with water and chloroform. The organic layer was separated, washed with water, dried and evaporated. The oily residue was purified by column chromatography (silica gel 500 g, eluent chloroform-methanol-ammonium hydroxide 95-5-0.5) to give a pure oil (8.1 g, 0.018 mole) which was dissolved in ethanol (120 ml) and treated with 4-acetaminobenzoic acid (3.23 g, 0.018 mole). After evaporation of the solvent, the solid residue was crystallized from ethyl acetate to give pure **4g** (10.0 g, 53%, mp 120-121°).

Anal. Calcd. for $C_{29}H_{34}BrN_5O_6$: C, 55.42; H, 5.45; N, 11.14. Found: C, 55.27; H, 5.40; N, 11.01.

1-[[1-(3-Bromo-5-isoxazolyl)-1-ethylidenjiminooxy]-3-[2-(3,4-dimethoxyphenyl)ethylamino]-2-propanol 4-Acetaminobenzoate **4h**.

Compound **4h** was similarly prepared as a solid in a yield of 55% (mp 105-106° from ethyl acetate).

Anal. Calcd. for $C_{27}H_{33}BrN_4O_8$: C, 52.18; H, 5.35; N, 9.01. Found: C, 52.28; H, 5.29; N, 8.92.

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