Synthesis of New Isoxazole Aminoalcohols

D. Chiarino*, M. Fantucci, A. Sala and C. Veneziani

Zambon Group Research Laboratories,
Bresso, Milan, Italy

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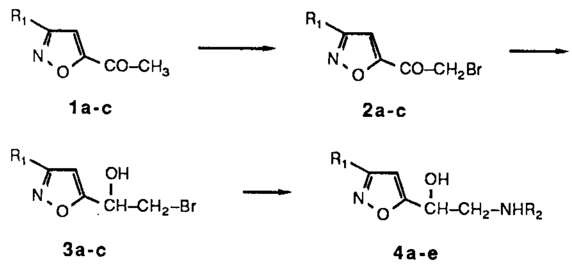
The preparation of new 1-isoxazolyl-2-amino-1-ethanol derivatives is described starting from the corresponding 1-isoxazolylethanones. It is also reported the synthesis of 1-(5-isoxazolyloxy)-3-amino-2-propanol compounds starting from the corresponding 5-haloisoxazoles and the obtainment of 1-(3-isoxazolyloxy)-3-amino-2-propanol compounds starting from the methyl 3-hydroxy-5-isoxazolecarboxylate.

J. Heterocyclic Chem., **25**, 337 (1988).

In a previous paper [1] we reported the synthesis of a new series of isoxazole aminoethanols and the pharmacological evaluation of their β_2-mimetic properties. Among the derivatives displaying marked activity, compound 1-(3-bromo-5-isoxazolyl)-2-(*t*-butylamino)ethanol (Broxaterol) was further developed as potential bronchodilatory agent in the asthma therapy [2,3].

In continuing our program of chemical study and utilization of potentially active β-adrenergic isoxazoles, we were interested to verify how the nature and the position of the substituent at the heterocyclic ring could influence the activity preparing a number of compounds bearing substituents which would be different from the previously described [1] 3-halo and 3-alkoxy groups. Thus we synthetized some 1-isoxazolyl-2-amino-1-ethanol and 1-isoxazolyloxy-3-amino-2-propanol compounds in which the substituent and the aminoalcoholic chain at the isoxazole nucleus were rotated.

Scheme 1

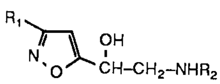


1-3 R_1

a CH_3
b C_6H_5
c $COOC_2H_5$

Scheme 1 illustrates the synthetic approach used for the preparation of 1-(5-isoxazolyl)-2-amino-1-ethanol deriva-

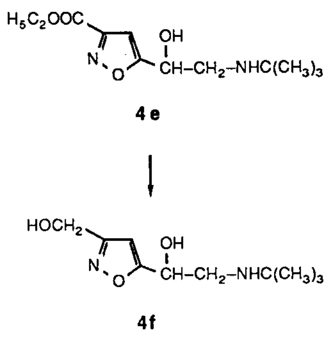
Table 1



Compound	R_1	R_2	Yield [a], %	Mp, °C (Crystallization solvent) [b]	Molecular Formula	Analysis, % (Calcd./Found) C	H	N
4a	CH_3	*t*-C_4H_9	27	177-178	$C_{10}H_{18}N_2O_2$	51.17	8.16	11.93
				(A)	.HCl	51.35	8.37	11.88
4b	CH_3	*i*-C_3H_7	25	165-166	$C_9H_{16}N_2O_2$	59.49	6.93	11.56
				(A)	.$C_9H_9NO_3$ [c]	59.28	7.02	11.52
4c	C_6H_5	*t*-C_4H_9	40	126-127	$C_{15}H_{20}N_2O_2$	69.20	7.74	10.76
				(B)		68.98	7.81	10.69
4d	C_6H_5	*i*-C_3H_7	44	121-122	$C_{14}H_{18}N_2O_2$	68.27	7.37	11.37
				(B)		68.37	7.55	11.15
4e	$COOC_2H_5$	*t*-C_4H_9	36	86-87	$C_{12}H_{20}N_2O_4$	56.23	7.87	10.93
				(C)		56.29	7.98	11.00
4f	CH_2OH	*t*-C_4H_9	37	79-80	$C_{10}H_{18}N_2O_3$	56.05	8.47	13.07
				(D)		56.10	8.60	13.03

[a] Yields of **4a-e** calculated from **1a-c**; yield of **4f** calculated from **4e**. [b] Crystallization solvents: A = acetonitrile, B = 2-propanol, C = *n*-hexane, D = 2-propanol-isopropyl ether. [c] 4-Acetaminobenzoic acid.

Scheme 2

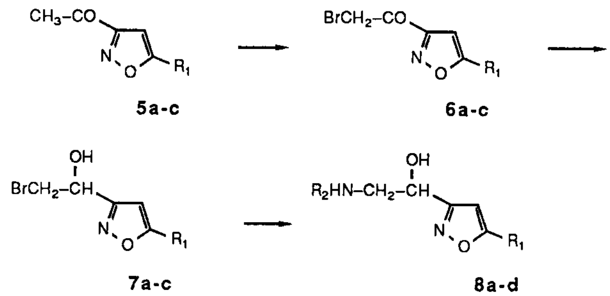


tives **4a-e**. Known ketones **1a-c** [4,5,6] were treated with bromine in carbon tetrachloride in the presence of a catalytic amount of acetic acid to give bromoketones **2a-c**. Crude derivatives **2a-c** were reduced with sodium borohydride in methanol affording crude bromohydrins **3a-c** which were treated with the appropriate alkylamine in ethanol to obtain desired compounds **4a-e**. Derivative **4e** was reduced with sodium borohydride in ethanol affording compound **4f** (Scheme 2). Analytical data of derivatives **4a-f** are presented in Table 1; ^{1}H-nmr of these molecules are reported in Table 6.

Scheme 3 shows the preparation of 1-(3-isoxazolyl)-2-amino-1-ethanol compounds **8a-d**. Ketones **5a-c** were obtained as already described [5,7,8]; the three steps of this synthesis were carried out as previously reported for compounds **4a-e**. Analytical data of derivatives **8a-d** are presented in Table 2; ^{1}H-nmr data of these molecules are listed in Table 6.

Scheme 4 illustrates the synthesis of 1-(4-isoxazolyl)-2-amino-1-ethanol compounds **12a-g** starting from known

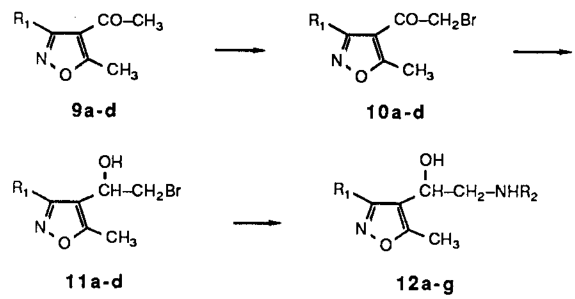
Scheme 3



5-7 R_1

a CH_3
b C_6H_5
c CH_2OH

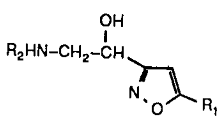
Scheme 4



9-11 R_1

a C_6H_5
b $2\text{-}ClC_6H_4$
c $2\text{-}Cl\text{-}6\text{-}FC_6H_3$
d $COOC_2H_5$

Table 2

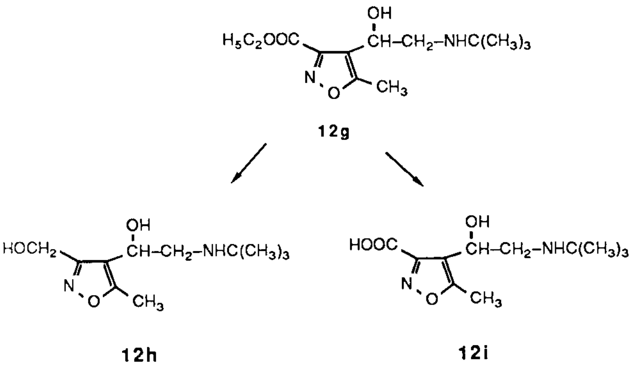


Compound	R_1	R_2	Yield [a], %	Mp, °C (Crystallization solvent) [b]	Molecular Formula	Analysis, % (Calcd./Found) C	H	N
8a	CH_3	$t\text{-}C_4H_9$	36	146-147 (A)	$C_{10}H_{18}N_2O_2$ .HCl	51.17 / 51.45	8.16 / 8.34	11.94 / 11.80
8b	CH_3	$i\text{-}C_3H_7$	33	143-144 (A)	$C_9H_{16}N_2O_2$ .HCl	48.98 / 48.89	7.76 / 7.96	12.69 / 12.64
8c	C_6H_5	$i\text{-}C_3H_7$	38	207-208 (A)	$C_{14}H_{18}N_2O_2$ .HCl	59.46 / 59.54	6.77 / 6.82	9.91 / 10.01
8d	CH_2OH	$q\text{-}C_3H_7$	37	107-108 (B)	$C_9H_{16}N_2O_3$ $.C_7H_6O_2$ [c]	59.61 / 59.83	6.88 / 7.09	8.69 / 8.83

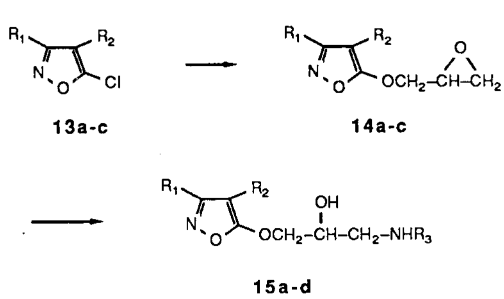
[a] Yields calculated from **5a-c**. [b] Crystallization solvents: A = 2-propanol, B = 2-propanol-ethyl ether. [c] Benzoic acid.

ketones **9a-d** [6,9,10,11] and adopting the experimental conditions described for derivatives **4a-e**. Compound **12g** was used as starting material for the preparation of derivatives **12h** and **12i**; the former was obtained by reduction with sodium borohydride in ethanol and the latter by hydrolysis with aqueous hydrochloric acid (Scheme 5). Analytical data of derivatives **12a-i** are illustrated in Table 3; [1]H-nmr data of these molecules are reported in Table 6.

Scheme 5



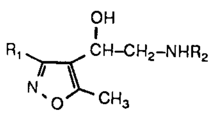
Scheme 6



13-14	R_1	R_2
a	C_6H_5	H
b	4-ClC_6H_4	H
c	CH_3	$COOC_2H_5$

Scheme 6 illustrates the preparation of 1-(5-isoxazolyloxy)-3-amino-2-propanol compounds **15a-d** starting from known chloro derivatives **13a-c** [12,13,14] which were treated with glycidol in *N,N*-dimethylformamide in the presence of sodium hydride. Resulting epoxydes **14a-c**, reacting with the appropriate alkylamine in ethanol, gave

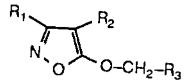
Table 3



Compound	R_1	R_2	Yield [a], %	Mp, °C (Crystallization solvent) [b]	Molecular Formula	Analysis, % (Calcd./Found) C	H	N
12a	C_6H_5	*t*-C_4H_9	45	201-201 dec	$C_{16}H_{22}N_2O_2$	66.97	6.85	6.79
				(A)	.$C_7H_6O_3$ [c]	67.23	6.90	6.75
12b	C_6H_5	*i*-C_3H_7	47	157-158 dec	$C_{15}H_{20}N_2O_2$	66.31	6.58	7.03
				(B)	.$C_7H_6O_3$ [c]	66.12	6.49	7.10
12c	2-ClC_6H_4	*t*-C_4H_9	40	201-202 dec	$C_{16}H_{21}ClN_2O_2$	61.81	6.09	6.27
				(A)	.$C_7H_6O_3$ [c]	62.10	6.18	6.31
12d	2-ClC_6H_4	*i*-C_3H_7	59	161-162 dec	$C_{15}H_{19}ClN_2O_2$	61.04	5.82	6.47
				(B)	.$C_7H_6O_3$ [c]	61.10	5.82	6.36
12e	2-Cl-6-FC_6H_3	*t*-C_4H_9	38	202-203 dec	$C_{16}H_{20}ClFN_2O_2$	59.42	5.64	6.02
				(C)	.$C_7H_6O_3$ [c]	59.48	5.56	5.88
12f	2-Cl-6-FC_6H_3	*i*-C_3H_7	64	164-165 dec	$C_{15}H_{18}ClFN_2O_2$	58.60	5.37	6.21
				(C)	.$C_7H_6O_3$ [c]	58.38	5.27	5.98
12g	$COOC_2H_5$	*t*-C_4H_9	52	87-88	$C_{13}H_{22}N_2O_4$	57.76	8.20	10.36
				(D)		57.90	8.35	10.18
12h	CH_2OH	*t*-C_4H_9	35	109-110	$C_{11}H_{20}N_2O_3$	57.87	8.83	12.27
				(E)		57.79	8.99	12.27
12i	COOH	*t*-C_4H_9	86	206-207 dec	$C_{11}H_{18}N_2O_4$	54.53	7.49	11.56
				(E)		54.24	7.55	11.64

[a] Yields of **12a-g** calculated from **9a-d**; yields of **12h-i** calculated from **12g**. [b] Crystallization solvents: A = ethanol, B = 2-propanol, C = acetonitrile, D = *n*-hexane, E = water. [c] 4-Hydroxybenzoic acid.

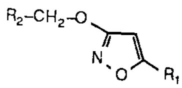
Table 4



Compound	R_1	R_2	R_3	Yield [a], %	Mp, °C (Crystallization solvent) [b]	Molecular Formula	Analysis, % (Calcd./Found) C	H	N
14a	C_6H_5	H	2-oxiranyl	60	102-103	$C_{12}H_{11}NO_3$	66.35	5.10	6.45
					(A)		66.46	4.97	6.49
14b	4-ClC_6H_4	H	2-oxiranyl	69	94-95	$C_{12}H_{10}ClNO_3$	57.27	4.00	5.57
					(A)		57.33	4.03	5.55
14c	CH_3	$COOC_2H_5$	2-oxiranyl	63	71-72	$C_{10}H_{13}NO_5$	52.86	5.77	6.16
					(B)		52.70	5.80	6.11
15a	C_6H_5	H	$CHOHCH_2NH$-*t*-C_4H_9	61	127-128	$C_{16}H_{22}N_2O_3$	66.18	7.64	9.65
					(C)		66.18	7.53	9.56
15b	C_6H_5	H	$CHOHCH_2NH$-*i*-C_3H_7	60	99-100	$C_{15}H_{20}N_2O_3$	65.20	7.29	10.14
					(C)		65.26	7.23	10.15
15c	4-ClC_6H_4	H	$CHOHCH_2NH$-*t*-C_4H_9	65	133-134	$C_{16}H_{21}ClN_2O_3$	59.16	6.52	8.62
					(C)		59.23	6.67	8.65
15d	CH_3	$COOC_2H_5$	$CHOHCH_2NH$-*t*-C_4H_9	34	65-66	$C_{14}H_{24}N_2O_5$	55.98	8.05	9.33
					(A)		55.77	8.20	9.41

[a] Yields of **14a-c** calculated from **13a-c**; yields of **15a-d** calculated from **14a-c**. [b] Crystallization solvents: A = isopropyl ether, B = *n*-hexane, C = acetonitrile.

Table 5



Compound	R_1	R_2	Yield [a], %	Mp, °C (Crystallization solvent) [b]	Molecular Formula	Analysis, % (Calcd./Found) C	H	N
17a	$COOCH_3$	2-oxiranyl	36	69-70	$C_8H_9NO_5$	48.24	4.55	7.03
				(A)		48.18	4.60	7.09
17b	CH_2OH	2-oxiranyl	69	oil	$C_7H_9NO_4$	49.12	5.30	8.18
						49.00	5.41	8.30
18a	$COOCH_3$	$CHOHCH_2NH$-*t*-C_4H_9	58	129-130	$C_{12}H_{20}N_2O_5$	46.68	6.85	9.07
				(B)	.HCl	46.70	7.02	9.19
18b	$CONH_2$	$CHOHCH_2NH$-*t*-C_4H_9	40	163-164	$C_{11}H_{19}N_3O_4$	51.35	7.44	16.33
				(C)		51.32	7.41	16.37
18c	CH_2OH	$CHOHCH_2NH$-*i*-C_3H_7	64	113-114	$C_{10}H_{18}N_2O_4$	52.16	7.90	12.17
				(A)		52.10	7.82	12.21

[a] Yield of **17a** calculated from **16**; yield of **17b** calculated from **17a**; yields of **18a,c** calculated from **17a,b**; yield of **18b** calculated from **18a**. [b] Crystallization solvents: A = 2-propanol, B = acetonitrile, C = water.

the desired compounds **15a-d**. Analytical data of derivatives **14a-c** and **15a-d** are reported in Table 4; ^{1}H-nmr data of compounds **15a-d** are shown in Table 6.

The synthetic route used to obtain the 1-(3-isoxazolyloxy)-3-amino-2-propanol compounds **18a-c** is described in Scheme 7. Known methyl 3-hydroxy-5-isoxazolecarboxylate **16** [15] was treated with epibromohydrin in *N,N*-dimethylformamide in the presence of sodium hydride. Resulting epoxyde **17a**, by reaction with *t*-butylamine in ethanol, afforded compound **18a** which was transformed into amide **18b** with methanolic ammonia. Intermediate **17a** was also reduced with sodium borohydride in methanol obtaining epoxyde **17b** which was treated with isopropylamine in ethanol to give desired compound **18c**.

Scheme 7

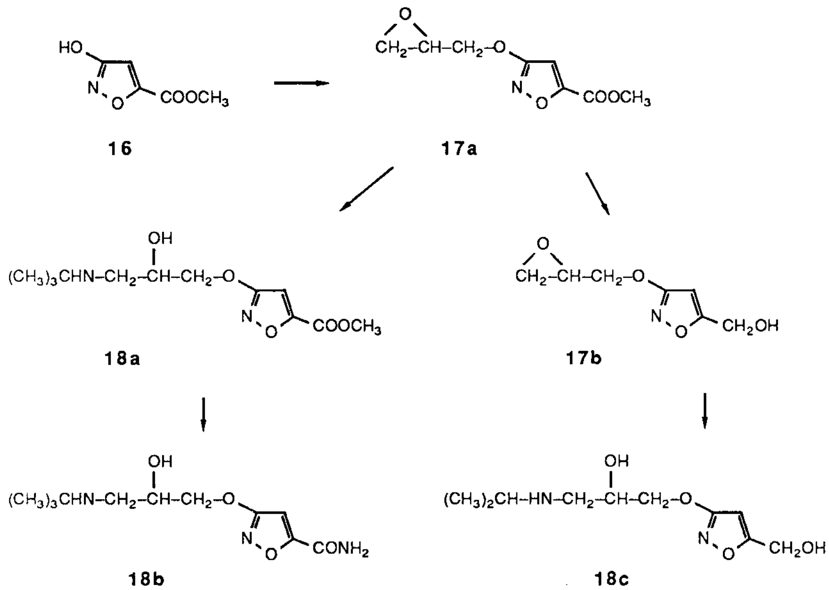


Table 6

^{1}H-NMR Data of Compounds **4a-f**, **8a-d**, **12a-i**, **15a-d** and **18a-c**

Compound	δ (ppm) Dimethyl-d_6 sulfoxide [a]
4a	1.36 (s, 9H), 2.28 (s, 3H), 2.9-3.5 (m, 2H), 5.30 (m, 1H), 6.52 (s, 1H)
4b	1.17 (d, 6H), 2.10 (s, 3H), 2.23 (s, 3H), 2.8-3.4 (m, 3H), 5.02 (m, 1H), 6.35 (s, 1H), 7.78 (q, 4H)
4c	1.06 (s, 9H), 2.95 (d, 2H), 4.73 (t, 1H), 7.00 (s, 1H), 7.5-8.3 (m, 5H)
4d	1.01 (d, 6H), 2.7-3.2 (m, 2H), 4.90 (t, 1H), 7.07 (s, 1H), 7.5-8.3 (m, 5H)
4e	1.03 (s, 9H), 1.33 (t, 3H), 2.85 (d, 2H), 4.42 (q, 2H), 4.80 (t, 1H), 6.83 (s, 1H)
4f	1.52 (t, 3H), 4.50 (q, 2H), 7.5-7.9 (m, 3H), 8.1-8.5 (m, 2H), 9.06 (s, 1H)
8a	1.35 (s, 9H), 2.43 (s, 3H), 3.20 (m, 2H), 5.15 (m, 1H), 6.42 (s, 1H)
8b	1.31 (d, 6H), 2.44 (s, 3H), 3.0-3.7 (m, 3H), 5.19 (m, 1H), 6.43 (s, 1H)
8c	1.33 (d, 6H), 3.1-4.0 (m, 3H), 5.42 (m, 1H), 7.30 (s, 1H), 7.4-8.2 (m, 5H)
8d	1.27 (d, 6H), 2.9-3.6 (m, 3H), 4.67 (s, 2H), 5.17 (t, 1H), 6.58 (s, 1H), 7.3-8.4 (m, 5H)
12a	1.17 (s, 9H), 2.62 (s, 3H), 2.97 (d, 2H), 5.03 (t, 1H), 6.9-8.1 (m, 9H)
12b	1.12 (d, 6H), 2.64 (s, 3H), 2.8-3.7 (m, 3H), 5.02 (m, 1H), 6.8-8.5 (m, 9H)
12c	1.17 (s, 9H), 2.63 (s, 3H), 2.87 (d, 2H), 4.85 (t, 1H), 6.8-7.8 (m, 8H)
12d	1.07 (d, 6H), 2.57 (s, 3H), 2.7-3.3 (m, 3H), 4.73 (m, 1H), 6.9-7.9 (m, 8H)
12e	1.20 (s, 9H), 2.62 (s, 3H), 2.87 (d, 2H), 4.85 (m, 1H), 6.9-7.9 (m, 7H)
12f	1.08 (d, 6H), 2.62 (s, 3H), 2.8-3.5 (m, 3H), 4.94 (m, 1H), 6.8-7.8 (m, 7H)
12g	1.00 (s, 9H), 1.32 (t, 3H), 2.56 (s, 3H), 2.70 (s, 2H), 4.42 (q, 2H), 4.95 (t, 1H)
12h	1.00 (s, 9H), 2.42 (s, 3H), 2.72 (d, 2H), 4.52 (s, 2H), 4.63 (t, 1H)
12i	1.35 (s, 9H), 2.59 (s, 3H), 3.15 (m, 2H), 5.39 (t, 1H)
15a	1.13 (s, 9H), 2.67 (d, 2H), 3.6-4.6 (m, 3H), 6.00 (s, 1H), 7.3-8.1 (m, 5H)
15b	1.10 (d, 6H), 2.3-3.3 (m, 3H), 3.8-4.5 (m, 3H), 5.61 (s, 1H), 7.3-8.0 (m, 5H)
15c	1.13 (s, 9H), 2.73 (d, 2H), 3.9-4.6 (m, 3H), 5.87 (s, 1H), 7.4-8.0 (m, 4H)
15d	1.1-1.6 (m, 12H), 2.29 (s, 3H), 3.0-3.7 (m, 5H), 4.21 (q, 2H)
18a	1.35 (s, 9H), 3.10 (m, 2H), 4.32 (m, 3H), 4.92 (s, 3H), 7.17 (s, 1H)
18b	1.04 (s, 9H), 2.60 (m, 2H), 3.6-4.5 (m, 3H), 6.87 (s, 1H)
18c	1.35 (d, 6H), 2.85-3.75 (m, 3H), 4.33 (m, 3H), 4.62 (s, 2H), 6.24 (s,1H)

[a] TMS as internal standard.

These new isoxazole derivatives were investigated to determine their pharmacological activity, but no interesting β-adrenergic properties were found.

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded with a Varian EM-360L.

1-(3-Methyl-5-isoxazolyl)-2-(*t*-butylamino)ethanol Hydrochloride (**4a**).

To a stirred solution of **1a** (16.7 g, 0.133 mole) in carbon tetrachloride (87 ml) and acetic acid (3.8 ml) a solution of bromine (22.4 g, 0.14 mole) in carbon tetrachloride (70 ml) was added dropwise at 48° during 10 minutes. The colourless solution was poured into an ice-water mixture (300 ml) and the organic layer was separated, washed with water and dried. After evaporation of the solvent, oily **2a** was dissolved in methanol (280 ml), cooled at 10° and treated portionwise with sodium borohydride (2.27 g, 0.06 mole). The solution was stirred at room temperature for 1 hour, acidified to Congo Red with 2*N* hydrochloric acid and evaporated. The residue was poured into water and extracted with chloroform. The organic layer was separated, washed with water and dried. After evaporation of the solvent, oily **3a** was dissolved in ethanol (120 ml) and dropped into a stirred solution of *t*-butylamine (59.5 ml, 0.564 mole) in ethanol (600 ml). After refluxing for 12 hours, the solvent was evaporated and the residue was treated with 2*N* hydrochloric acid (100 ml) and ethyl ether (100 ml). The aqueous phase was separated and basified with potassium carbonate. The mixture was extracted with ethyl ether and 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 **4a** (8.4 g, 27%, mp 177-178°).

Compounds **4b-e**, **8a-d** and **12a-g** were similarly prepared.

1-(3-Hydroxymethyl-5-methyl-4-isoxazolyl)-2-(*t*-butylamino)ethanol (**12h**).

A stirred solution of **12g** (2.7 g, 0.01 mole) in ethanol (15 ml) was treated portionwise with sodium borohydride (0.61 g, 0.016 mole) at room temperature and the mixture was stirred at 40° for 3 hours. After cooling, the solution was acidified to Congo Red with 2*N* hydrochloric acid and evaporated. The residue was diluted with water, basified with potassium carbonate and extracted with ethyl ether. The organic layer was separated, dried and evaporated and the solid residue was crystallized from 2-propanol-isopropyl ether to give pure **12h** (0.8 g, 35%, mp 109-110°).

Compound **4f** was similarly prepared.

4-[2-(*t*-Butylamino)-1-hydroxyethyl]-5-methyl-3-isoxazolecarboxylic Acid (**12i**).

A stirred solution of **12g** (2.7 g, 0.01 mole) in 5*N* hydrochloric acid (27 ml) was refluxed for 7 hours. The solvent was evaporated and the solid residue was crystallized from water to give pure **12i** as base (1.8 g, 74%, mp 205° dec).

5-(2,3-Epoxypropoxy)-3-phenylisoxazole (**14a**).

To a stirred mixture of 80% sodium hydride suspension in mineral oil (4.5 g, 0.15 mole) and *N,N*-dimethylformamide (100 ml) a mixture of 5-chloro-3-phenylisoxazole (27 g, 0.15 mole) and glycidol (11 g, 0.15 mole) was added dropwise during 3 hours at 100°. The reaction mixture was cooled at room temperature, poured into water (2000 ml) and extracted with chloroform. The organic layer was separated, washed with water, dried and evaporated. The solid residue was crystallized from isopropyl ether to give pure **14a** (31.5 g, 96%, mp 102-103°).

Compounds **14b-c** were similarly prepared.

1-(4-Chlorophenyl-5-isoxazolyloxy)-3-(*t*-butylamino)-2-propanol (**15c**).

A stirred mixture of **14b** (4.7 g, 0.0187 mole) and *t*-butylamine (6.8 g, 0.0927 mole) in ethanol (25 ml) was refluxed for 1 hour. The solution was evaporated and the solid residue was crystallized from acetonitrile to give pure **15c** (5.7 g, 82%, mp 134-135°).

Compounds **15a,b,d**, and **18a,c** were similarly prepared.

Methyl 3-(2,3-Epoxypropoxy)-5-isoxazolecarboxylate (**17a**).

To a stirred solution of methyl 3-hydroxy-5-isoxazolecarboxylate (93.7 g, 0.655 mole) in *N,N*-dimethylformamide (1000 ml) 80% sodium hydride suspension in mineral oil (27.6 g, 0.92 mole) was added portionwise at 0°. After stirring for 30 minutes, a solution of epibromohydrin (90 g, 0.656 mole) in *N,N*-dimethylformamide (130 ml) was dropped in and the resulting mixture was stirred at 50° for 24 hours. After cooling, the reaction mixture was poured into water (4500 ml) and extracted with ethyl ether. The organic layer was separated, washed with water, dried and evaporated. The solid residue was crystallized from 2-propanol tc give pure **17a** (47 g, 36%, mp 69-70°).

[3-(2,3-Epoxypropoxy)-5-isoxazolyl]methanol (**17b**).

To a stirred solution of **17a** (2 g, 0.01 mole) in methanol (55 ml) sodium borohydride (0.4 g, 0.0106 mole) was added portionwise at 10°. After stirring for 2 hours at room temperature, the mixture was diluted with water and the solvent was removed. The residue was extracted with ethyl ether; the organic layer was separated, dried and evaporated. The oily residue was purified by column chromatography (silica gel 150 g, eluent chloroform-methanol 98-2) to give pure **17b** as oil (1.2 g, 69%).

3-[3-(*t*-Butylamino)-2-hydroxypropoxy]-5-isoxazolecarboxamide (**18b**).

A solution of **18a** (1.2 g, 0.0039 mole) in 20% methanolic ammonia (25 ml) was stirred at room temperature for 24 hours. After evaporation of the solvent, the solid residue was crystallized from water to give pure **18b** (0.4 g, 40%, mp 163-164°).

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