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Original paper

β-Adrenergic antagonists: *N*-alkyl and *N*-amidoethyl (arylalkoxy)propanolamines related to propranolol*

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Summary — The synthesis and β-blocking activity of a new series of (arylalkoxy)propanolamines is described. These compounds are structural analogues of the aryloxypropanolamine β-blockers, in which different bridging moieties have been interposed between the aromatic ring and the ethereal oxygen atom. Although all compounds showed a considerable degree of β_1- or β_2-blockade, the (arylalkoxy) derivatives were 10—100 times less potent than the corresponding phenoxypropanolamines, thus suggesting that a spreading of the charge in the ethereal oxygen atom could enhance binding to the β-adrenoceptor. Cardioselectivity in the new series seems to be associated with a low pK_a value for the amine nitrogen. Thus, derivatives **5d**, **6d**, and **7d** are potent β_1-blockers with low β_2-activity.

Résumé — **Antagonistes β-adrénergiques: *N*-alkyl et *N*-amidoéthyl (arylalkoxy)propanolamines apparentés au propranolol.** *On décrit la synthèse et l'activité β-adrénolytique d'une nouvelle série d'(arylalkoxy)propanolamines. Nous avons incorporé diverses unités structurales dans ces analogues d'aryloxypropanolamines, pour séparer le noyau aromatique de l'atome d'oxygène de la fonction éther. Bien que tous les composés aient montré une activité antagoniste β_1 ou β_2 considérable, les dérivés d'(arylalkoxy)propanolamines sont de 10—100 fois moins actifs que les phénoxypropanolamines correspondantes. La délocalisation de la charge de l'atome d'oxygène pourrait ainsi améliorer la liaison des β-bloquants avec le récepteur adrénergique. Dans la série étudiée, la cardiosélectivité semble être en relation avec une diminution de la basicité de la fonction amine: par exemple, les dérivés **5d**, **6d** et **7d** sont des antagonistes β_1 puissants avec peu d'activité β_2.*

(arylalkoxy)propanolamines / β-blocking activity

Introduction

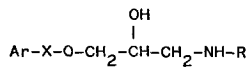
Aryloxypropanolamines are the most important structural class of β-adrenergic blockers and thousands of analogues of the first therapeutically useful drug in this series, propranolol **1**, have been synthesized [1]. Nevertheless, structure—activity relationships in the field of β-antagonists have not been completely established and there are few systematic studies aimed at ascertaining the essential features in the aryloxypropanolamine molecule [2].

It is known [3] that replacement of the ethereal oxygen atom of **1** by a methylene group reduces the potency markedly (>100 times), thus indicating that this atom is directly involved in the binding to the receptor by means of its unshared electrons. It is also possible that the electron-donor effect of the oxygen enhances the aryl group binding. However, some potent β-antagonists are known whose ethereal oxygen is not directly linked to the aromatic ring; examples of these 'non-classical' β-blockers are oxime ethers [4—6], such as falintolol **2** [7] and propanolamine esters [8—10], such as **3**. Recently, a series of compounds having the general structure **4** (*n* from 0 to 4) was reported [11] and the pA_2 value for the methylene analog ($n = 2$) of an aryloxypropanolamine was found to be surprisingly high (7.85, β_1). It was concluded that an ether oxygen in the side chain is not an absolute prerequisite for potent β-blockade, a major role being attributed to the distance between the aromatic ring and the aminoalcohol group. Nevertheless, other studies [12] pointed out the importance of an ethereal oxygen for the affinity to the β-receptor.

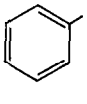
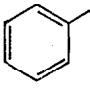
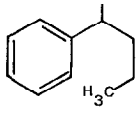
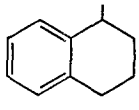
In light of the above results, we decided to investigate the effect upon β-blocking activity and β_1/β_2 selectivity of the interposition of aliphatic fragments between the aromatic ring and the oxypropanolamine side chain, without eliminating the ethereal oxygen. In this paper, we report a new series of (arylalkoxy)propanolamines in

*A preliminary account of this work was presented at the XXIIth Rencontres internationales de Chimie thérapeutique, Clermont-Ferrand, France, September 1986.

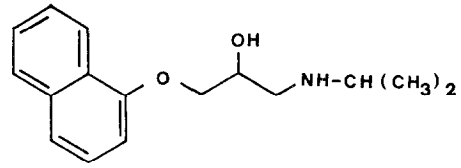
Table I. Physical properties and *in vitro* β-blocking activity of compounds **5—12.**



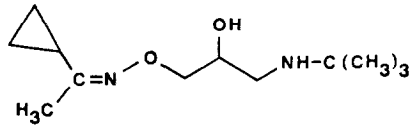
a. R= $-CH(CH_3)_2$
b. R= $-C(CH_3)_3$
c. R= $-CH_2-CH_2-NH-CO-CH_2-C_6H_5$
d. R= $-CH_2-CH_2-NH-CO-CH(CH_3)_2$

Compound	Ar-X-	Yield	mp, °C (purifn. solvent)	Formula [a]	pK_a	log D	log P	pA_2 [b] atrium (β_1)	pA_2 [b] trachea (β_2)	Selectivity β_1 / β_2
5a		75	105-107 (Me_2CO)	$C_{15}H_{23}NO_6$ [c]	9.46	-0.84	1.62	5.98 ± 0.24	5.96 ± 0.36	1.0
5b		76	91-93 (EtOH)	$C_{14}H_{23}NO_2$	9.49	-0.79	1.70	6.66 ± 0.16	7.95 ± 0.47	0.05
5c		45	91-93 (AcOEt)	$C_{20}H_{26}NO_3$	7.93	0.51	1.05	7.97 ± 0.34	7.67 ± 0.35	2.0
5d		58	124-128 (EtOH-Me_2CO)	$C_{18}H_{28}N_2O_7$ [c]	7.81	-0.25	0.63	7.04 ± 0.45	5.05 ± 0.30	98
6a		59	115-117 (EtOH-Me_2CO)	$C_{16}H_{25}NO_6$ [c]	9.04	-0.28	1.76	6.99 ± 0.50	6.32 ± 0.47	4.7
6b		50	164-167 (EtOH-Me_2CO)	$C_{17}H_{27}NO_6$ [c]	9.63	-0.13	2.51	7.10 ± 0.44	7.55 ± 0.29	0.4
6c		51	98-101 (AcOEt)	$C_{21}H_{28}N_2O_3$	7.65	0.5	1.24	7.94 ± 0.13	7.42 ± 0.35	3.3
6d		42	112-116 (AcOEt)	$C_{17}H_{28}N_2O_3$	7.83	0.03	0.95	7.13 ± 0.43	5.16 ± 0.62	93
7a		76	oil (bp 110-115°C/0.2)	$C_{15}H_{25}NO_2$	9.18	-0.64	1.54	6.60 ± 0.28	6.94 ± 0.38	0.5
7b		80	oil (bp 100-110°C/0.1)	$C_{16}H_{27}NO_2$	9.54	-0.37	2.18	7.18 ± 0.48	7.51 ± 0.43	0.5
7c		47	84-86 (AcOEt)	$C_{22}H_{30}N_2O_3$	7.81	0.77	1.62	7.73 ± 0.51	7.63 ± 0.38	1.3
7d		79	101-103 (EtOH-Me_2CO)	$C_{20}H_{32}N_2O_7$ [c]	7.89	0.32	1.25	7.40 ± 0.23	4.68 ± 0.35	525
8a		70	oil (bp 125-130°C/0.1)	$C_{14}H_{23}NO_3$	9.28	-0.67	1.63	6.77 ± 0.30	6.65 ± 0.30	1.3
8b		76	oil (bp 170-175°C/0.3)	$C_{15}H_{25}NO_3$	9.80	-0.45	2.35	inactive [d]	7.01 ± 0.58	---
8c		44	81-83 (AcOEt)	$C_{21}H_{28}N_2O_4$	8.03	-0.32	0.75	7.80 ± 0.24	7.45 ± 0.37	2.3
8d		51	119-122 (EtOH-Me_2CO)	$C_{19}H_{30}N_2O_4$ [c]	7.79	-0.38	0.48	7.58 ± 0.16	6.77 ± 0.60	6.5
9a		71	57-59 (hexane)	$C_{15}H_{23}NO_2$	9.27	-0.12	2.15	6.85 ± 0.19	6.62 ± 0.31	1.7
9b		77	49-51 (hexane)	$C_{16}H_{25}NO_2$	9.63	-0.34	2.29	6.81 ± 0.41	7.50 ± 0.26	0.2
9c		56	85-87 (AcOEt)	$C_{22}H_{28}N_2O_3$	7.91	0.80	1.76	7.67 ± 0.58	6.10 ± 0.30	37
9d		50	115-117 (EtOH-Me_2CO)	$C_{20}H_{30}N_2O_7$ [c]	7.69	-0.24	0.51	7.94 ± 0.36	6.79 ± 0.21	14
10a		53	110-112 (EtOH-Me_2CO)	$C_{18}H_{29}NO_6$ [c]	9.32	0.62	2.95	6.54 ± 0.26	6.55 ± 0.48	1.0
10b		43	110-112 (EtOH-Me_2CO)	$C_{19}H_{31}NO_6$ [c]	9.63	-0.34	2.29	6.81 ± 0.41	7.50 ± 0.26	0.2
10c		54	117-119 (AcOEt)	$C_{25}H_{34}N_2O_7$ [c]	7.51	0.32	0.94	7.68 ± 0.30	6.80 ± 0.27	7.6
10d		50	115-117 (EtOH-Me_2CO)	$C_{20}H_{30}N_2O_7$ [c]	7.69	-0.24	0.51	7.94 ± 0.36	6.79 ± 0.21	14
11a		36	128-130 (EtOH-Me_2CO)	$C_{18}H_{27}NO_6$ [c]	9.00	1.42	3.42	7.32 ± 0.15	7.23 ± 0.53	1.2
11b		56	70-72 (hexane)	$C_{17}H_{27}NO_2$	9.12	1.42	3.55	7.02 ± 0.46	7.76 ± 0.37	0.2
11c		37	68-70 (AcOEt)	$C_{23}H_{30}N_2O_3$	7.55	1.02	1.68	8.50 ± 0.37	7.77 ± 0.43	5.4
11d		60	130-134 (EtOH-Me_2CO)	$C_{21}H_{32}N_2O_7$ [c]	7.89	1.08	1.99	7.11 ± 0.26	7.81 ± 0.38	0.2
12a		78	89-92 (Et_2O)	$C_{12}H_{19}NO_2$	9.18	-0.71	1.47	8.77 ± 0.38	7.86 ± 0.34	8.1
12b		75	91-93 (hexane)	$C_{13}H_{21}NO_2$	9.46	-0.92	1.50	9.76 ± 0.25	9.87 ± 0.24	0.8
12c		51	110-112 (AcOEt)	$C_{19}H_{24}N_2O_3$	7.38	0.11	0.63	9.21 ± 0.19	8.53 ± 0.21	4.8
12d		45	120-123 (AcOEt)	$C_{15}H_{24}N_2O_3$	7.87	0.21	1.14	8.80 ± 0.23	8.12 ± 0.32	4.8
1 (propranolol)		---	----	----	9.13	0.79	2.92	8.60 ± 0.32	8.47 ± 0.25	1.5

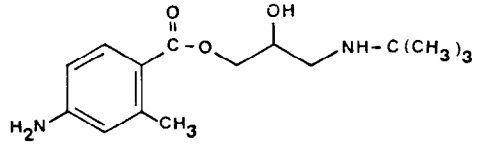
[a] All compounds were analyzed for C, H and N; analytical values were within 0.4% of calculated values.
[b] pA_2 values ± SD, for a minimum of 5 preparations. Four antagonist concentrations were tested in each. The slope of the Schild plot was 1 ± 0.15 in all cases.
[c] Oxalate salt.
[d] Agonist at 10^{-7} M.



1 propranolol



2 falintolol



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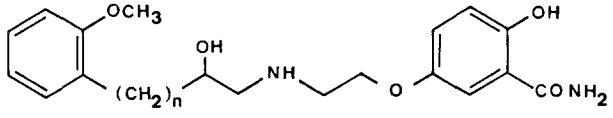


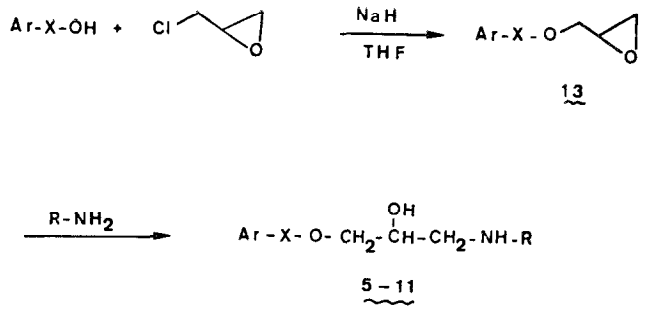
4

Scheme 1.

which the bridging moiety includes linear alkyl chains **5**—**7**, an ether **8**, an alkene **9**, a branched alkyl **10** and its cyclic derivative **11** (see structures in Table I). To ascertain the possible influence of structural changes at the opposite end of the molecule, all of these modifications have been combined with four types of *N*-substituents: two branched alkyl groups (series **a** and **b**) and two 2-amidoethyl substituents (series **c** and **d**). The latter are known to impart high β-blocking potency and cardioselectivity [13—16]. Four phenoxypropanolamines **12a**—**d** have also been synthesized and tested as standards for activity comparison; the β_1- and β_2-blocking potencies of compound **12a** are well known [17, 18].

Chemistry

Compounds **5**—**11** were obtained from the sodium salts of the corresponding alcohols, in a two-step procedure very similar to that used [2] for the synthesis of aryloxypropanolamines (see Scheme 2). The salts were generated *in situ* by NaH treatment and made to react with excess epichlorohydrin. Glycidyl ethers **13**—**19** were purified by vacuum distillation and treated with the appropriate amine in ethanol or 2-propanol solution, to give the desired (arylalkoxy)propanolamines. The pure ethers **5**—**11** were isolated as free bases or oxalate salts from the crude reaction mixtures (Table I).



Scheme 2.

Pharmacology

The biological profiles of the compounds listed in Table I at β_1- and β_2-adrenoceptors were assessed on electrically stimulated guinea pig left atria and on tracheal chains, respectively. Isoproterenol was used as the agonist; detailed testing procedures have been reported previously [19]. The potency of drugs is expressed as pA_2 calculated according to Van Rossum [20].

Results and Discussion

Except for diether **8b** on atrium, all compounds displayed a considerable degree of competitive β-blockade, with pA_2 values ranging from 4.5 (**7b**, β_2) to 8.5 (**11c**, β_1). Interposition of an alkyl chain between the phenyl ring and the ethereal oxygen (compounds **5a**—**d**—**7a**—**d**) proved to be clearly detrimental to activity, as compared with the directly linked structures **12a**—**d**. Figs. 1 and 2 are plots of the β_1- and β_2-blocking potencies in relation to the

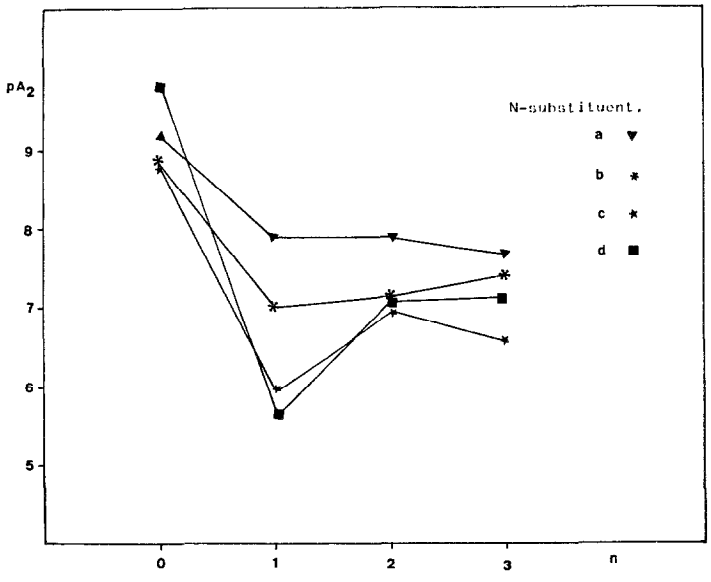
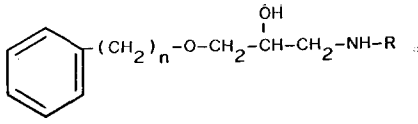


Fig. 1. Plot of β_1 blocking potency for compounds **12** and **5**—**7** in relation to the length of the X bridging moiety. See structure of the R substituents in Table I.



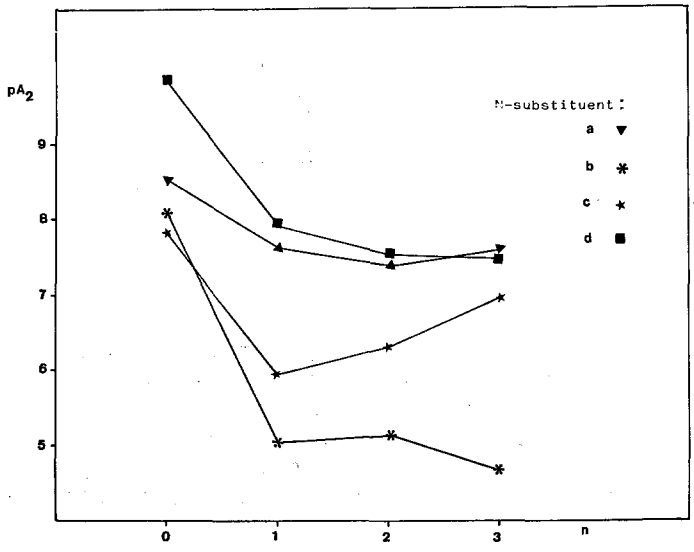


Fig. 2. Plot of β_2 blocking potency for compounds **12** and **5**—**7** in relation to the length of the X bridging moiety. See structure of the R substituents in Table I.

length of the bridging alkyl unit, for the four series of homologues **5**—**7** and **12**, differing in the *N*-substituent.

As a general trend, after a sharp fall of 2—3 pA_2 units on going from the (aryloxy)- to the (arylalkoxy)propanolamines, the potency remains approximately constant for each series. This relative lack of sensitivity towards molecular variations of the (arylalkoxy)propanolamine derivatives also becomes apparent if the mean pA_2 values for all compounds in each **a**—**d** series of *N*- substituents are considered (Table II). Thus, standard deviations turned out to be very small, except for the tracheal activity of compounds bearing an *N*-(2-amidoethyl) group. The higher mean pA_2 on atrium found for series **c** and **d** compounds than those for the *N*-isopropyl or *N*-*tert*-butyl derivatives seem to lend support to the hypothesis that *N*-amidoalkyl substituents enhance β-blocker cardioselectivity [13—16]. In fact, our series contains a very selective compound, the phenylpropoxy derivative **7d**, which is almost inactive on the trachea and fairly potent on the heart.

Compounds **10a**—**d** can be considered both as open analogues of **11a**—**b** and as α-propyl-substituted derivatives of benzyloxypropanolamines **5a**—**d**. Although these structural changes are rather important, the β-blocking activities of **10**, **11** and **5** did not differ significantly. However, a clear decrease in β-blockade is associated with reduction of naphthalene ring A in propranolol (*cf.* activity of **1** and **11a**), a result which again indicates the need of a direct contact between the aryl and oxygen for potent β-antagonism.

Taken as a whole, the above results suggest that the (arylalkoxy)propanolamines act upon β-adrenoceptors in a partially non-specific way. This prompted us to determine the representative physical constants (pK_a and log*P*) for compounds **5**—**12** and **1**. However, we were unable to find any statistically significant correlation between β-blocking potency and these physical parameters; inclusion of a $(\log P)^2$ term did not improve correlation. Very active compounds, such as **12b** have pK_a and log*P* values almost identical to those found for **5a**, one of the poorest β-blockers within the series. On the other hand, very lipophilic derivatives, such as **11a**, **b**, are of the same order of β_1-potency as compounds with $\log P < 1$, such as **8d** or **9d**.

The only general trend which emerged from this study was the consistently lower basicity of the *N*-amidoethyl compounds (series **c** and **d**, mean $pK_a = 7.75 \pm 0.19$) as compared with the *N*-isopropyl and N-*tert*-butyl derivatives (series **a** and **b**, mean $pK_a = 9.36 \pm 0.22$), due to the electron-withdrawing effect of the amide group. This result is in good agreement with the hypothesis that cardiac receptors are associated with a more hydrophilic environment than tracheal receptors [7, 21]. Indeed, low log*P* values are found for cardioselective compounds (*cf.* **5d**, **6d**, **7d**, **9d** and **10d**), whereas all compounds having $\log P > 2$ are non-selective or slightly β_2-selective.

In a recent study [22], it was found that the net negative charge on the ethereal oxygen atom of propranolol **1** and oxime ether β-blockers related to **2** is of the same order of magnitude, about —0.15 to —0.20. In contrast, the oxygen atom in an almost inactive (cyclopropylmethoxy)-propanolamine derivative had a net charge of —0.39. We can thus postulate an explanation for the moderate β-blocking potency found in (arylalkoxy)propanolamines **5**—**11**, as these compounds may be expected to have very negative ether functions, with no spreading of the charge. Compounds **8a**—**d**, although containing two oxygen atoms,

Table II. Mean pA_2 values ($\pm$SD) for compounds **5**—**11**.

N—R substituent	Mean pA_2 (β_1)	Mean pA_2 (β_2)
a: —$CH(CH_3)_2$	6.70±0.38	6.61±0.38
b: —$C(CH_3)_3$	6.94±0.18[a]	7.61±0.30
c: —CH_2CH_2—NH—CO—$CH_2C_6H_5$	7.90±0.27	7.24±0.60
d: —CH_2CH_2—NH—CO—$CH(CH_3)_2$	7.42±0.33	6.35±1.30

[a]Compound **8b** is not included.

one of them conjugated with the phenyl group, do not show more activity than their methylene analogues **7a—c**, thus suggesting that the observed fall in β-blockade could be due to an electrostatic repulsion between the negative ether group (still present in **8a—d**) and the adrenoceptor.

In conclusion, the postulated bioisosterism between the aromatic ring in adrenergic arylethanolamines and the $ArOCH_2$—, —CO—OCH_2— and C=N—OCH_2— fragments in (aryloxy)propanolamines, (aroyloxy)propanolamines, and oxime ethers, respectively [10], cannot be extended to (arylalkoxy) derivatives, since this group differs significantly in its electronic properties. Nevertheless, selected members of this class are rather potent β-blockers; for example, the phenylacetamide-substituted tetralin **11c** or the benzyloxy derivatives **5b** and **5c** have pA_2 values which are in the same order of magnitude as that found for propranolol.

Experimental protocols

Chemistry

Melting points were determined on a Büchi apparatus and are uncorrected. All compounds have ^1H NMR spectra consistent with the assigned structure; for compounds **5—12** belonging to series **c** and **d**, ^{13}C NMR spectra were also recorded (Varian FT-200 apparatus). Compounds **5—12** were purified by column chromatography on silica gel 60 (Merck, 0.063—0.200 mm) prior to distillation or crystallization. Analytical samples were dried *in vacuo* and were free of significant impurities on thin—layer chromatography (TLC) (Merck silica gel plates with F_{254} indicator). All microdistillations were made in a Büchi GKR-50 Kugelrohr apparatus. Solutions in organic solvents were dried over anhydrous sodium sulfate and evaporated *in vacuo* (rotating evaporator). Elemental analyses were performed by Departamento de Química Orgánica (C.S.I.C.), Barcelona, and agreed with theoretical values to within ± 0.4%.

General procedure for the synthesis of (arylalkoxy)methyloxiranes ***13—19***
A solution of 10 mmol of the appropriate primary or secondary alcohol in 20 ml of dry tetrahydrofuran (THF) was added under nitrogen to a stirred suspension of 10 mmol of sodium hydride (50% oil dispersion, previously washed with hexane) and 20 mmol of epichlorohydrin in 50 ml of dry THF. The mixture was stirred at reflux for 2 h, cooled, poured into 200 ml of ice—water, and extracted with ether (3 × 50 ml). The organic layers were washed with brine, dried and evaporated to afford crude epoxides **13—19**, which were purified by distillation. NMR spectra showed characteristic multiplets at δ 2.3 (OCH_2 oxirane), 2.8 (OCH) and 3.4 (OCH_9).
2-(Benzyloxymethyl)oxirane ***13***. Yield 66%; bp: 75—85°C, 0.5 mm Hg Anal. ($C_{10}H_{12}O_2$) C, H.
2-[(2-Phenylethoxy)methyl]oxirane ***14***. Yield 73%; bp: 86—90°C, 0.5 mm Hg. Anal. ($C_{11}H_{14}O_2$) C, H.
2-[(3-Phenylpropoxy)methyl]oxirane ***15***. Yield 75%; bp: 105—110°C, 0.1 mm Hg. Anal. ($C_{12}H_{16}O_2$) C, H.
2-[(2-Phenoxyethoxy)methyl]oxirane ***16***. Yield 61%; bp: 100—105°C, 0.2 mm Hg. Anal ($C_{11}H_{14}O_3$) C, H.
2-[(Cinnamyloxy)methyl]oxirane ***17***. Yield 62%; bp: 105—108°C, 0.3 mm Hg. Anal. ($C_{12}H_{14}O_2$) C, H.
2-[(1-Phenylbutoxy)methyl]oxirane ***18***. Yield 56%; bp: 70—75°C, 0.3 mm Hg. Anal. ($C_{13}H_{18}O_2$) C, H.
2-[(1,2,3,4-Tetrahydro-1-naphthoxy)methyl]oxirane ***19***. Yield 61%; bp: 95—105°C, 0.4 mm Hg. Anal. ($C_{13}H_{16}O_2$) C, H.

General procedure for the synthesis of N-*isopropyl and* N-tert-*butyl substituted compounds* ***5—11***
A solution of 10 mmol of the appropriate oxirane **13—19** and 70 mmol of isopropylamine or *tert*-butylamine in 100 ml of absolute ethanol was stirred at reflux for 2 h. The solvent was evaporated *in vacuo*, the residue was taken up with 100 ml of a 1 N solution of hydrochloric acid and the resulting solution was washed with ether (3 × 30 ml). The aqueous layers were made alkaline with a 2 N sodium hydroxide solution and extracted with dichloromethane (3 × 50 ml). Evaporation of the dried extracts afforded crude aminoalcohols **5—11**, which were purified by chromatography and distillation or crystallization (see Table I).

General procedure for the synthesis of N-*(2-phenylacetamido)ethyl and* N-*(2-isobutyramido)ethyl substituted compounds* ***5—11***
A solution of 10 mmol of the epoxide **13—19** and 10 mmol of *N*-(2-aminoethyl)phenylacetamide or *N*-(2-aminoethyl)isobutyramide in 100 ml of 2-propanol was stirred at reflux under nitrogen for 16 h. The solvent was evaporated at reduced pressure and the (amidoethyl)-aminoalcohols were isolated as in the above procedure.

Physical determinations
pK_a. The K_a values were measured by potentiometry following the directions given by Albert and Serjeant [23]. Solutions of test compounds were made 0.01 N in a 1:1 mixture of methanol and water and titrated under nitrogen atmosphere and at 25°C with 0.1 N hydrochloric acid.
*log*D and *log*P. Partition coefficients were determined at 25°C according to Hellenbrecht *et al.* [24]. We used presaturated 1-octanol and phosphate buffer, pH = 7.0; 3—5 mg samples were used. Separation of the organic layer was effected by centrifugation at 3000 rpm and the UV readings were made with the aqueous layer, at the maximum wavelength for each compound (from 227 to 290 nm). *D* values were calculated as $D = [(A_1 - A_2)/(A_2 \cdot f)]$, where A_1 is the absorbance of the original solution, A_2 is the absorbance after octanol extraction, and f is the volume ratio octanol/buffer. The log*P* values were calculated as $\log P = [\log(D/1 - \alpha)]$, where α is the ionization constant for each compound.

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