Synthesis of New Oxazolidine, Oxazolidin-2-one and Perhydro-1,4-oxazine Derivatives of Arylethanolamine as Potential *beta*$_3$-Adrenoceptor Agonists

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The synthesis of new cyclic compounds, arylethanolamine derivatives, with potential *beta*$_3$-adrenoceptor agonist selectivity, which are associated with thermogenesis and regulation of insulin release, are described. Oxazolidine, oxazolidin-2-one, and perhydro-1,4-oxazine derivatives were obtained. The preliminary evaluation of the pharmacological effects of some of the synthesized compounds showed an activation of lypolysis in rat adipocytes with potency and efficiency similar to that observed for other accredited *beta*$_3$-adrenergic agonists.

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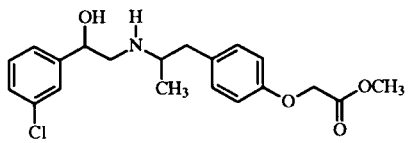
The sympathetic nervous system plays an important role in the lipid metabolism because catecholamines have a marked lipolytic effect on fat cells through different subtypes of *beta*-adrenoceptors [1]. In addition, adrenergic effects on blood vessels, altering the microcirculation and blood flow, have been involved in the catecholamine-induced lipolysis in fat cells [2]. The *beta*-adrenoceptor is coupled to the adenylate-cyclase in a positive way, increasing the intracellular level of cAMP and subsequently, activating the "hormone-sensitive lipase" [3].

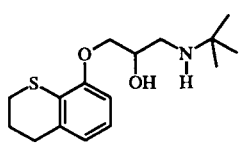
On the other hand, information is rather scarce concerning the "atypical" *beta*-adrenoceptor (*beta*$_3$-adrenoceptor), which has been involved in thermogenic and lipolytic activities of the adipose tissue [4,5]. In this context, the data obtained from isolated adipocytes could be extrapolated to physiopathological conditions such as obesity.

In order to obtain new potential *beta*$_3$-agonists, we focused our study on the cyclization of the pharmacophore ethanolamine, which is present in compounds such as **1** (BRL 35135), **11** (Tertatolol), and CGP-12177 a well-known *beta*$_3$-agonist (Figure 1).

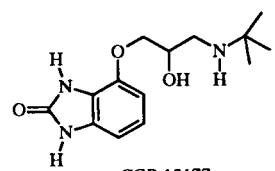


BRL 35135

1



Tertatolol



CGP-12177

11

Figure 1

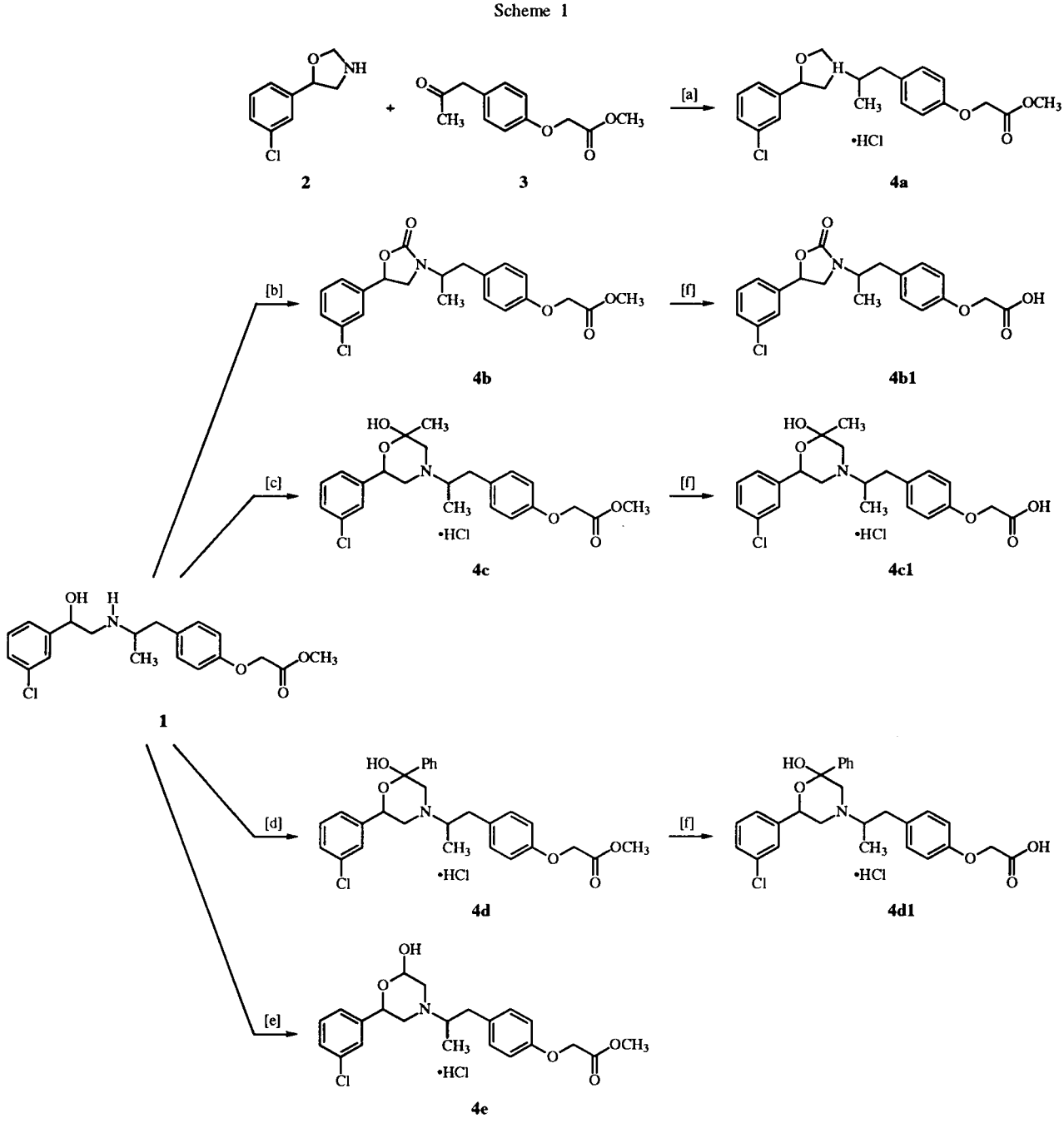
The synthetic pathway to the cyclic derivatives of BRL 35135 **1** is outlined in Scheme 1. The method of Cantello *et al.* [4] was used in the preparation of **1** and **3**. Compound **1** was obtained as a diastereomeric mixture (^{13}C nmr analysis).

The oxazolidine derivative methyl 4-[2-[5-(3-chlorophenyl)-2-oxazolidin-3-yl]propyl]phenoxyethanoate hydrochloride **4a** (Scheme 1) was obtained using conditions essentially identical to the method of Reiffen *et al.* [6], using now the oxazolidine derivative of 2-amine-1-(3-chlorophenyl)-1-ethanol **2**, which was synthesized using the method of Delgado *et al.* [7]. The oxazolidin-2-one derivatives methyl 4-[2-[5-(3-chlorophenyl)-2-oxooxazolidin-3-yl]propyl]phenoxyethanoate monohydrate **4b**, 3-[1-(4-methylphenyl)ethyl]-5-phenyloxazolidin-2-one **6b** (Scheme 2) and 5-[(3,4-dihydro-2*H*-1-benzothiopyran-8-yl)oxymethyl]-3-(1,1-dimethylethyl)oxazolidin-2-one **12a** (Scheme 4) were synthesized with the cyclization reagent *N,N'*-carbonyldiimidazole [8].

The perhydro-1,4-oxazines **4c**, **4d**, **6c**, **6d**, **12b** and **12c** were obtained by treatment with α-haloketones (chloroacetone, chloromethyl phenyl ketone) [9] using the described conditions (Schemes 1, 2 and 4). For synthesis of the hemiacetal derivatives **4e**, **6e** and **12d**, a combined methodology using Borch's and Agami's methods [10,11], with ethanedial as the electrophilic reagent and sodium cyanoborohydride as the reductor, was developed.

The esters methyl 4-[2-[5-(3-chlorophenyl)-2-oxooxazolidin-3-yl]propyl]phenoxyethanoate monohydrate **4b**, methyl 4-[2-[6-(3-chlorophenyl)-2-hydroxy-2-methylperhydro-1,4-oxazin-4-yl]propyl]phenoxyethanoate hydrochloride **4c**, and methyl 4-[2-[6-(3-chlorophenyl)-2-hydroxy-2-phenylperhydro-1,4-oxazin-4-yl]propyl]phenoxyethanoate hydrochloride **4d**, were saponified with potassium hydroxide (2*M*)/ethanol to prevent hydrolysis of the cyclic structures (Scheme 1).

Scheme 1

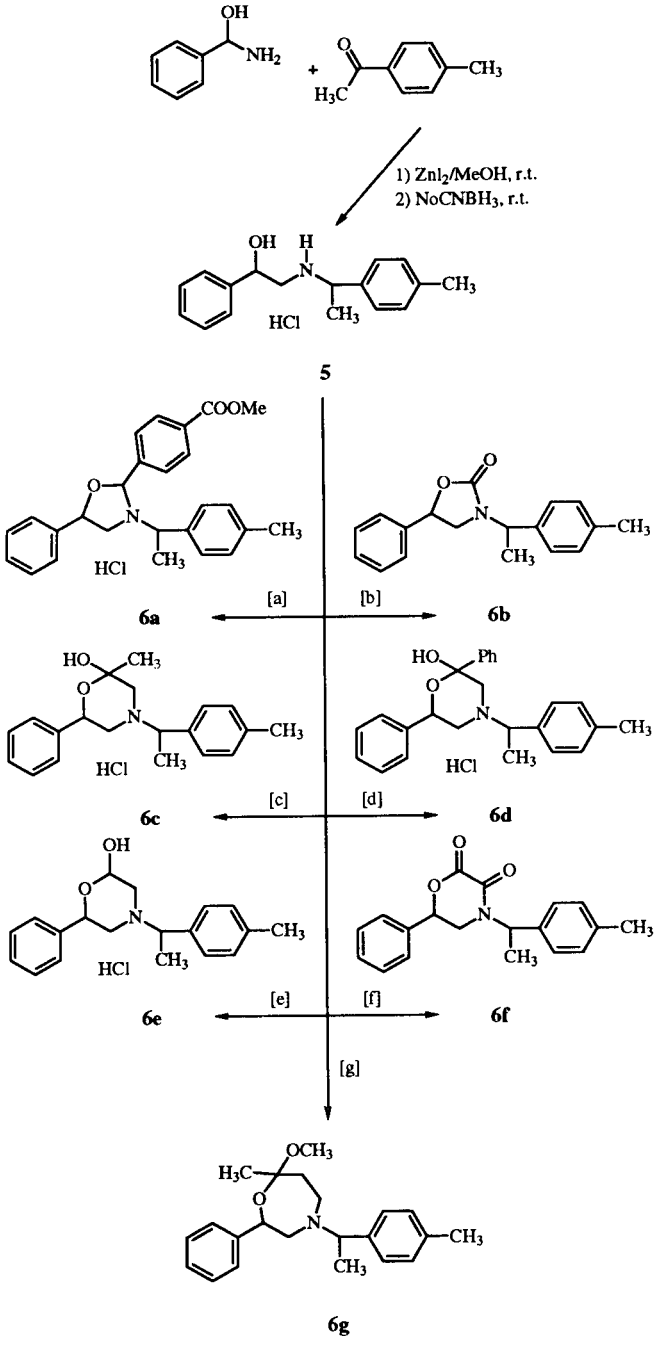


[a] 1) ZnI_2/MeOH, r.t. 2) $NaCNBH_3$, r.t.; [b] CDI/THF, reflux; [c] $ClCH_2COCH_3$, KCO_3H, Cl, Acetone, reflux; [d] $ClCH_2COPh$, KCO_3H, KI, Acetone, reflux; [e] Et_3N, OHC-CHO, $NaCNBH_3$, MeOH, r.t.; [f] KOH (2M)/EtOH.

2-[1-(4-Methylphenyl)ethylamino]-1-phenylethanol hydrochloride **5** was prepared following the reductive amination method [12], using zinc iodide as Lewis acid. The compound was obtained as a diastereomeric mixture (^1H nmr and ^{13}C nmr analyses). The synthetic pathway to the cyclic derivatives of **5** is outlined in Scheme 2. Treatment of **5** with methyl 4-formylbenzoate in the Dean-Stark system [13] provided the oxazolidine derivative methyl 4-[5-phenyl-3-[1-(4-methylphenyl)ethyl]oxazolidin-2-yl]benzoate hydrochloride **6a**. The chromatographic resolution (silica gel, petroleum ether:ethyl ether (80:20)) yielded three fractions corresponding with the different diastereomers or diastereomeric mixtures of **6a**.

The 1,4-oxazepine derivative **6g** was obtained from **5**

Scheme 2



[a] Methyl 4-formylbenzoate, ZnI_2, Toluene, reflux; [b] CDI/THF, reflux; [c] $ClCH_2COCH_3$, K_2CO_3, KI, ZnI_2, Acetone, reflux; [d] $ClCH_2CO$-Ph, KCO_3H, Acetone, reflux; [e] OHC-CHO, $NaCNBH_3$, MeOH, r.t.; [f] ClOCCOCl, Et_3N, THF, r.t.; [g] $CH_3COCH{=}CH_2$, MeOH, Toluene, reflux.

using butenone as the Michael substrate. The perhydro-1,4-oxazine-2,3-dione derivatives 4-[1-(4-methylphenyl)ethyl]-6-phenylperhydro-1,4-oxazin-2,3-dione **6f** (Scheme 2) and 6-[(3,4-dihydro-2*H*-1-benzothiopiran-8-yl)oxymethyl]-4-(1,1-dimethyl)perhydro-1,4-oxazine-2,3-dione **12f** (Scheme 4) were obtained using the method of Lida *et al.* [14].

The synthesis of 2-(2-hydroxy-2-phenylethylamino)-*N*-(4-methoxyphenyl)ethanamide **9** and the cyclic derivatives *N*-(4-methoxyphenyl)-2-(5-phenyloxazolidin-3-yl)ethanamide **10a**, *N*-(4-methoxyphenyl)-2-(5-phenyloxazolidin-3-yl)propanamide **10b** and *N*-(4-methoxyphenyl)-2-[(5-(3-chlorophenyl)oxazolidin-3-yl]propanamide **10c** was performed following a nucleophilic substitution method [5], shown in Scheme 3. The compounds **10a** and **10b** were obtained as diasteromeric mixtures (^1H nmr and ^{13}C nmr analysis).

The synthesis of Tertatolol (1-[(3,4-dihydro-2*H*-1-benzotiopiran-8-yl)oxy]-3-(1,1-dimethylethylamine)-2-propanol) **11** derivatives **12a-12f** is shown in Scheme 4. 6-[(3,4-Dihydro-2*H*-1-benzothiopiran-8-yl)oxymethyl]-4-(1,1-dimethylethyl)perhydro-1,4-oxazine-3-one **12e** was obtained in moderate yield by reflux of **11** with bromoacetyl bromide [15].

Preliminary studies with a limited number of the synthesized compounds revealed a lipid mobilizing activity in adipose tissue, which was compared to two *beta*-adrenergic agonists with known affinity for $beta_3$-adrenoceptors such as BRL 35135 [4] and ICI 198157 [5]. The synthesis and development of compounds with $beta_3$-adrenergic properties may be useful in the treatment of obesity [16] because these products have shown activities on lipid mobilization and thermogenesis [17] with apparently less undesirable effects than those observed with other lipolytic substances such as $beta_1$ and $beta_2$-adrenergic agonists [18].

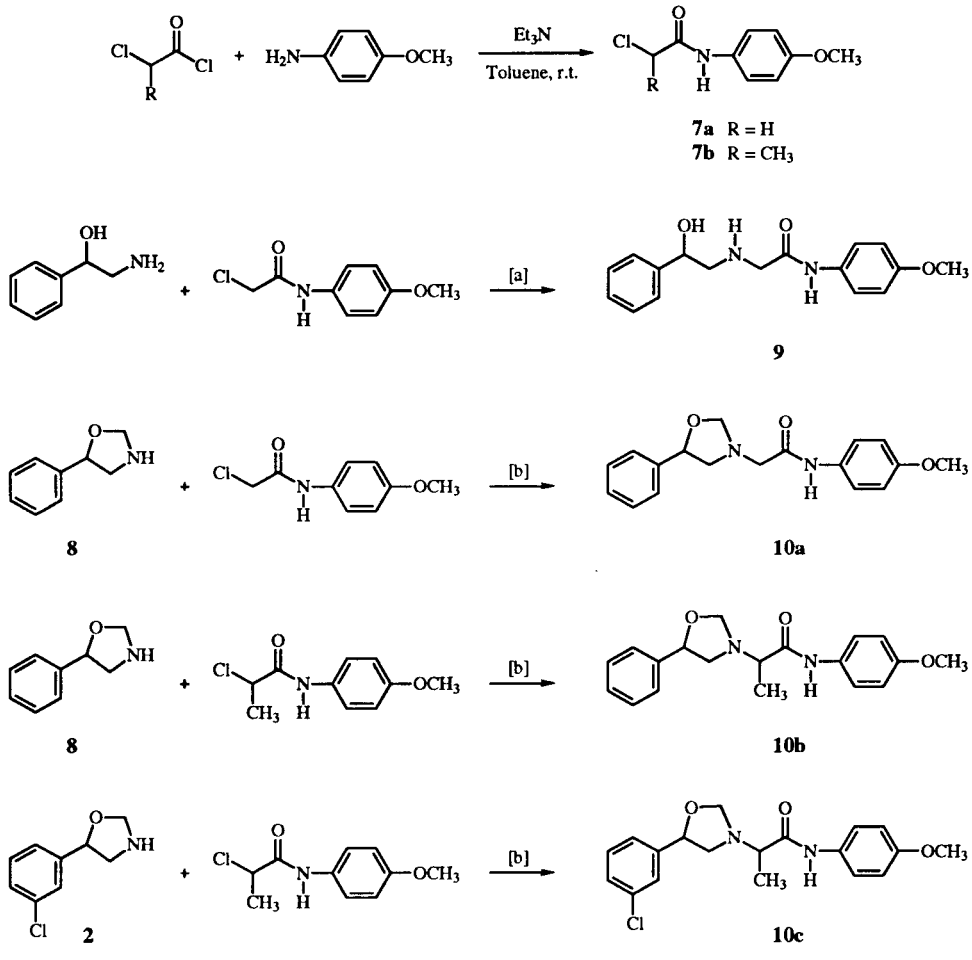
EXPERIMENTAL

Melting points were determined on a Mettler FP82 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1600 series FTIR apparatus, using potassium bromide tablets for solid products and sodium chloride plates for liquid products; the frequencies are expressed in cm^{-1}. Mass spectra were recorded on a Hewlett-Packard Model 5988A spectrometer. The ^1H nmr and ^{13}C nmr spectra were recorded on a Bruker Model AC-200E (200 MHz) with tetramethylsilane as the internal reference, in the indicated solvent. Chemical shifts are given in ppm (δ). The reactions were followed by analytical tlc in Kieselgel 60 F 254 with the appropriate eluents; spots were visualized by uv or iodine vapor. The analytical purity of the compounds were determined on a hplc apparatus Waters 600E/Waters 994 Programmable Photodiode Array Detector. Elemental analyses were obtained from vacuum-dried samples (over phosphorus pentoxide at 3-4 mm Hg, 24 hours at about 60-80°) on a Carlo Erba elemental analyzer Model 1106.

5-(3-chlorophenyl)oxazolidine (**2**).

A dissolution of 2-amino-1-(3-chlorophenyl)-1-ethanol (2.00 g, 11.66 mmoles) and formaldehyde 37% (1.5 ml, 20.01 mmoles) in tetrahydrofuran (20 ml) was stirred at reflux temper-

Scheme 3



[a] Et_3N, Toluene, r.t.; [b] K_2CO_3, KI, Ethanol, reflux.

ature for 8 hours and at room temperature overnight. The tetrahydrofuran was eliminated, and the residue was dissolved in chloroform (30 ml) and washed with water (2 x 15 ml). The organic phase was evaporated until dry, and the oil obtained was chromatographed and eluted with dichloromethane:methanol (95:5). An orange oil was obtained (1.75 g, 79%); ^{1}H nmr (deuterioacetone) (hydrochloride): δ 3.00-4.00 (m, 3H), 5.00 (d, J = 5.0 Hz, 1H), 5.20 (m, 1H), 5.45 (d, J = 5.1 Hz, 1H), 7.41 (s, 4H); ir (sodium chloride) (free base): 3371 (NH), 1036 (CO), 878, 786 cm^{-1}.

Methyl 4-[2-[5-(3-Chlorophenyl)oxazolidin-3-yl]propyl]phenoxyethanoate Hydrochloride (**4a**).

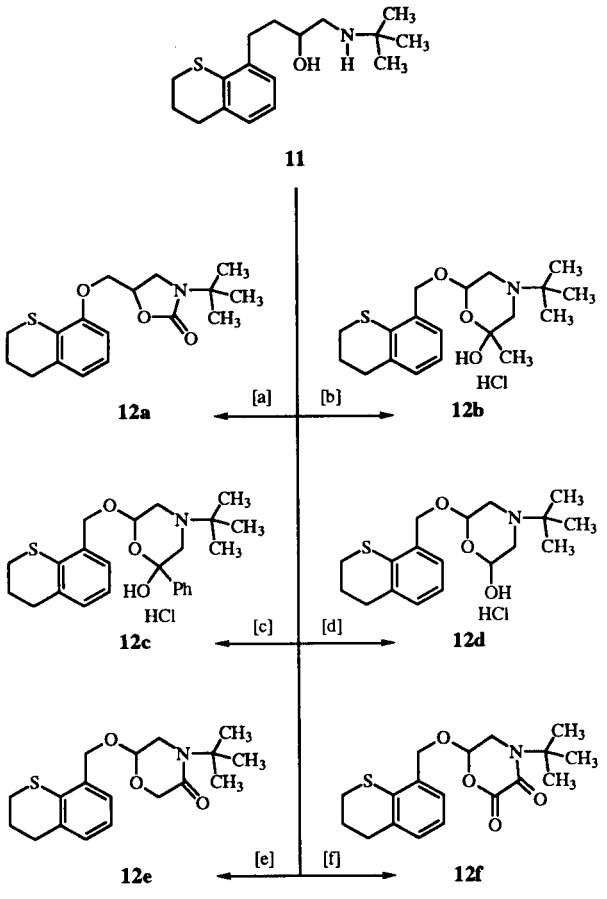
In a flask with nitrogen atmosphere and molecular sieves 4 Å, 5-(3-chlorophenyl)oxazolidine **2** (1.00 g, 5.45 mmoles), methyl 2-[4-(2-oxopropyl)phenoxy]ethanoate **3** (1.21 g, 5.45 mmoles) and methanol saturated with hydrogen chloride (10 ml) were introduced. Zinc iodide (0.86 g, 2.69 mmoles) and methanol (10 ml) were added *via* syringe. The mixture was stirred at room temperature for 24 hours. Sodium cyanoborohydride (1.04 g, 16.56 mmoles) and methanol (13 ml) were added, and the mixture was stirred for 24 hours at room temperature. The solvent was evaporated. Water (30 ml) was added and the mixture was extracted with ethyl acetate (3 x 40 ml). The organic layer was dried, and the solvent was evaporated. The resulting oil was chromatographed (silica gel, dichloromethane:methanol (99:1)). The oil was dissolved in ethanol, and ethyl ether saturated with hydrogen chloride (5 ml) was added to obtain a semi-solid, which was obtained as a solid in high *vacuo* (0.66 g, 31%), mp 54-55°; ^{1}H nmr (deuterioacetone) (free base): δ 1.07 (m, 3H), 2.35-3.00 (m, 4H), 3.76 (s, 3H), 4.10 (m, 1H), 4.72 (s+d, 3H), 4.90 (m, 1H), 5.61 (d, 1H), 6.80 (d, 2H), 7.06-7.52 (m, 6H); ^{13}C nmr (deuterioacetone) (free base): δ 19.0, 19.5 (*C*-C-N), 41.1, 41.5 (*C*-C-N), 50.9 (*C*-OOC), 51.1, 51.4 (*C*-N), 64.5 (O-*C*-COO), 65.0, 65.2 (*C*-N), 70.5, 70.8 (*C*-O), 96.0 (N-*C*-O), 113.6 to 156.2 (aromatic carbons), 168.7 (-*C*OO); ir (sodium chloride): 2750 (NH^+), 1753 (C=O), 1211 and 1078 (CO) cm^{-1}; ms: m/z 208, 207, 192, 179, 168, 77.

Anal. Calcd. for $C_{21}H_{25}Cl_2NO_4 \cdot 1/2H_2O$: C, 57.93; H, 5.98; N, 3.22. Found: C, 57.93; H, 5.81; N, 2.87.

Methyl 4-[2-[5-(3-Chlorophenyl)-2-oxooxazolidin-3-yl]propyl]-phenoxyethanoate Monohydrate (**4b**).

A mixture of **1** (1.00 g, 2.64 mmoles), *N,N'*-carbonyldiimida-

Scheme 4



[a] CDI, THF, reflux; [b] CH_3COCH_2Cl, K_2CO_3, KI, Acetone, reflux; [c] $ClCH_2CO$-Ph, KCO_3H, KI, Acetone, reflux; [d] OHC-CHO, $NaCNBH_3$, MeOH, r.t.; [e] 1) $BrCH_2COBr$, THF, reflux, 2) Na, reflux; [f] ClOCCOCl, Et_3N, r.t.

zole (0.51 g, 3.14 mmoles) and tetrahydrofuran (5 ml) was stirred at reflux for 48 hours. The solvent was evaporated. Ethyl acetate (50 ml) was added and the organic layer was washed successively with hydrogen chloride (1%) (2 x 20 ml) and brine (2 x 20 ml). The organic layer was dried, and the solvent was evaporated to give an oil. The oil was chromatographed (silica gel, dichloromethane:methanol (99:1)) to provide a yellow oil (0.75 g, 65%); ^1H nmr (deuterioacetone): δ 1.15 (d, 3H), 2.60-2.80 (m, 2H), 3.27 (m, 1H), 3.67 (s, 3H), 3.89 (m, 2H), 4.61 (s, 2H), 5.38 (m, 1H), 6.72-7.34 (m, 8H); ^{13}C nmr (deuterioacetone): δ 17.0, 17.3 (*C*-C-N), 39.1, 39.2 (*C*-C-N), 47.6, 48.4 (*C*-N), 50.1, 51.0 (*C*-N), 51.6 (*C*-OOC), 65.2 (O-*C*-COO), 73.4, 73.7 (*C*-O), 114.7 to 156.7 (aromatic carbons), 156.9 (N-*C*O-O), 169.2 (*C*OO); ir (sodium chloride): 1754 (C=O ester), 1746 (C=O), 1204 and 1085 (CO) cm^{-1}; ms: m/z 224, 206, 180.

Anal. Calcd. for $C_{21}H_{24}ClNO_6$: C, 59.79; H, 5.69; N, 3.32. Found: C, 59.92; H, 5.36; N, 3.21.

Methyl 4-[2-[6-(3-Chlorophenyl)-2-hydroxy-2-methylperhydro-1,4-oxazine-4-yl]propyl]phenoxyethanoate Hydrochloride (**4c**).

In a flask with a nitrogen atmosphere, compound **1** (1.50 g, 3.96 mmoles), chloroacetone (0.5 ml, 5.97 mmoles), potassium bicarbonate (1.20 g, 11.98 mmoles), potassium iodide (0.30 g, 1.80 mmoles) and acetone (10 ml) were introduced. The mixture was refluxed under nitrogen for 24 hours. The solution obtained was cooled and filtered. The solvent was evaporated. The residue was chromatographed (silica gel, gradient dichloromethane to dichloromethane:methanol (99:1)). Ether saturated with hydrogen chloride (5 ml) was added to the flask containing the oil, and the mixture was dissolved in absolute ethanol (5 ml). The mixture was cooled to 0° and stirred. A mixture of carbon tetrachloride and petroleum ether was added in order to better the precipitation of the hydrochloride. The solid which separated was filtered and then washed with petroleum ether, giving **4c** (0.60 g, 89%), mp 77-78°; ^1H nmr (deuterioacetone): δ 1.38 (d, 3H), 1.47 and 1.51 (two singlets that correspond to the different stereoisomers, 3H), 2.75 (m, 1H), 3.00-3.80 (m, 9H), 4.25 (q, 1H), 4.64 (s, 2H), 5.63 (m, 1H), 6.80-7.60 (m, 8H), 12.08 (ws, 1H, HCl); ^{13}C nmr (deuterioacetone): δ 11.0, 12.3, 14.2, 15.4 (*C*-C-N), 27.1, 27.2 (*C*-C-O), 34.0, 36.3, 36.4, 38.0 (*C*-C-N), 47.3, 51.2, 51.6, 51.9 (*C*-N), 53.2, 53.5, 54.0, 55.3 (*C*-N), 57.0 (*C*-OOC), 61.2 (O-*C*-COO), 64.7, 64.8, 65.6, 65.7 (*C*-N), 68.0, 68.2, 69.2, 72.2 (*C*-O), 94.5, 94.6, 97.4 (hemiacetal carbons), 115.4 to 158.0 (aromatic carbons), 167.0, 169.2, 169.7, 171.0 (*C*OO); ir (potassium bromide): 3400 (OH), 2344 and 2299 (NH^+), 1753 (C=O), 1206 and 1069 (CO) cm^{-1}; ms: m/z 254, 236, 210.

Anal. Calcd. for $C_{23}H_{29}Cl_2NO_5$: C, 58.72; H, 6.17; N, 2.98. Found: C, 58.70; H, 6.46; N, 3.05.

Methyl 4-[2-[6-(3-Chlorophenyl)-2-hydroxy-2-phenylperhydro-1,4-oxazine-4-yl]propyl]phenoxyethanoate Hydrochloride (**4d**).

In a flask with a nitrogen atmosphere, **1** (1.50 g, 3.96 mmoles), chloromethyl phenyl ketone (0.63 g, 4.07 mmoles), potassium bicarbonate (1.20 g, 11.98 mmoles), potassium iodide (0.30 g, 1.80 mmoles) and acetone (10 ml) were introduced. The mixture was refluxed under nitrogen for 24 hours. The solution obtained was cooled and filtered. The solvent was evaporated. The residue was chromatographed (silica gel, gradient dichloromethane to dichloromethane:methanol (99:1)). Ether saturated with hydrogen chloride (5 ml) was added to the flask containing the oil and the mixture was dissolved in absolute ethanol (5 ml). The yellow oil was digested with carbon tetrachloride:petroleum ether to give yellow needles (0.65 g, 87%), mp 81-82°; ^1H nmr (deuterioacetone): δ 1.24 (d, 3H), 2.75 (m, 1H), 3.00-3.90 (m, 9H), 4.13 (q, 1H), 4.63 (s, 2H), 5.90 (m, 1H), 6.81 (d, J = 7 Hz, 2H), 7.20-7.85 (m, 11H), 10.20 (ws, 1H, HCl); ^{13}C nmr (deuterioacetone): δ 10.4, 12.2, 14.0, 14.9 (*C*-C-N), 34.4, 36.0, 36.1, 37.4 (*C*-C-N), 51.0, 51.7, 52.5, 52.6 (*C*-N), 53.7, 53.9, 54.8, 56.0 (*C*-N), 58.0 (*C*-OOC), 61.0 (O-*C*-COO), 64.6, 64.7, 65.3, 65.4 (*C*-N), 68.5, 68.6, 69.4, 69.5 (*C*-O), 95.4, 98.6 (hemiacetal carbons), 115.1 to 157.7 (aromatic carbons), 168.9 (*C*OO); ir (potassium bromide): 3421 (OH), 2580 (NH^+), 1754 (C=O), 1203 and 1079 (CO) cm^{-1}; ms: m/z 330, 298, 272.

Anal. Calcd. for $C_{23}H_{29}Cl_2NO_5$: C, 63.16; H, 5.83; N, 2.63. Found: C, 63.21; H, 5.86; N, 2.16.

Methyl 4-[2-[6-(3-Chlorophenyl)-2-hydroxyperhydro-1,4-oxazine-4-yl]propyl]phenoxyethanoate Hydrochloride (**4e**).

A mixture of **1** (1.21 g, 3.19 mmoles), triethylamine (1.4 ml, 10.07 mmoles), ethanedial 40% (0.54 ml, 3.54 mmoles), sodium cyanoborohydride (0.62 g, 9.87 mmoles) and methanol was

added to a dry flask with septum and nitrogen bubbler, containing molecular sieves. It was stirred for 24 hours, then ethanedial 40% (0.54 ml, 3.54 mmoles) and zinc iodide (catalytic quantity) were added. It was stirred for 6 days. Part of the methanol was removed *in vacuo*. The residue was taken up in a 2*N* sodium hydroxide solution (10 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was extracted with hydrochloric acid (2*N*). The aqueous layer was basified and extracted with ethyl acetate (3 x 20 ml). The combined extracts were dried, evaporated *in vacuo*, and purified by column chromatography (silica gel, dichloromethane:methanol (99.5:0.5)). Two fractions were obtained. After vacuum evaporation an oil was obtained for each one. They were dissolved in ethanol, and ethanol saturated with hydrogen chloride (5 ml) was added. They were digested with a mixture of carbon tetrachloride and petroleum ether. The solid which separated was filtered and then washed with petroleum ether. Fraction I (highest retardation factor) (0.13 g, 9%), had mp 59-61°; ^{1}H nmr (deuterioacetone) (free base): δ 0.90 (d, 3H), 2.10-3.10 (m), 3.67 (s, 3H), 4.61 (s+m, 3H), 4.97 (m, 1H), 6.77 (d, J = 8 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 7.38 (m, 4H); ^{13}C nmr (deuterioacetone) (free base): δ 13.2, 13.7 (*C*-C-N), 37.8, 37.9 (*C*-C-N), 51.3 (*C*-OOC), 53.0, 53.9 (*C*-N), 55.5, 56.9 (*C*-N), 60.8, 61.1 (*C*-N), 64.8 (O-*C*-COO), 69.7, 75.1 (*C*-O), 90.4, 94.1 (hemiacetal carbons), 114.2 to 156.3 (aromatic carbons), 169.0 (*C*OO); ir (potassium bromide): 3222 (OH), 2582 (NH^+), 1752 (C=O), 1381 (CH_3), 1203 and 1080 (CO) cm^{-1}; ms: m/z 240, 222, 207, 196.

Anal. Calcd. for $C_{22}H_{27}Cl_2NO_5 \cdot 3/4H_2O$: C, 56.23; H, 6.07; N, 2.98. Found: C, 56.27; H, 6.14; N, 2.96.

Fraction II (lowest retardation factor) (0.12 g, 8%), had mp 61-62°; ^{1}H nmr (deuterioacetone) (free base): δ 0.94 (d, 3H), 2.39-3.60 (m, 8H), 3.67 (s, 3H), 4.42 (m, 1H), 4.64 (s, 2H), 4.84 (m, 1H), 6.81 (d, J = 7 Hz, 2H), 7.11 (d, J = 7 Hz, 2H), 7.33 (m, 4H); ^{13}C nmr (deuterioacetone) (free base): δ 14.0, 14.5 (*C*-C-N), 38.0, 39.5 (*C*-C-N), 51.5 (*C*-OOC), 52.5, 53.0 (*C*-N), 56.5, 57.5 (*C*-N), 60.0, 61.5 (*C*-N), 65.2 (O-*C*-COO), 67.6, 71.9 (*C*-O), 91.0, 94.5 (hemiacetal carbons), 114.7 to 157.0 (aromatic carbons), 169.5 (*C*OO); ir (potassium bromide): 3375 (OH), 2436 (NH^+), 1753 (C=O), 1383 (CH_3), 1202 and 1079 (CO) cm^{-1}; ms: m/z 240, 222, 207, 196.

Anal. Calcd. for $C_{22}H_{27}Cl_2NO_5 \cdot 3/4H_2O$: C, 56.23; H, 6.07; N, 2.98. Found: C, 56.19; H, 6.55; N, 3.12.

General Hydrolysis of Esters.

A suspension of the ester (1.80 mmoles) in 2*M* potassium hydroxide (9.4 ml) and ethanol (9.4 ml) was stirred at room temperature for 30 minutes. The solution was evaporated *in vacuo*. The oil obtained was neutralized with hydrogen chloride and extracted with ethyl acetate. The solvent was dried and evaporated. The residue corresponds to the desired compound.

4-[2-[5-(3-Chlorophenyl)-2-oxooxazolidin-3-yl]propyl]phenoxyethanoic Acid (**4b1**).

Hydrolysis of the ester was carried out following the general method. A transparent oil was obtained (0.57 g, 81%); ^{1}H nmr (deuterioacetone): δ 1.14 (superposed doublets that correspond to different stereoisomers, 3H), 2.66-2.80 (m, 2H), 3.28 (t, J = 7.5 Hz, 1H), 3.93 (t, J = 8.7 Hz, 1H), 4.15 (q, 1H), 4.61 (s, 2H), 5.42 (q, J = 5.5 Hz, 1H), 6.50 (ws, 1H), 6.77 (superposed doublets that correspond to different stereoisomers, J = 8 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 7.32-7.43 (m, 4H); ^{13}C nmr (deuterioacetone): δ 16.6, 16.9 (*C*-C-N), 38.7, 38.9 (*C*-C-N), 47.3, 48.1 (*C*-N), 50.0, 50.8 (*C*-N), 64.6 (O-*C*-COO), 73.2, 73.5 (*C*-O), 114.4 to 156.7 (aromatic carbons), 156.8 (N*C*OO), 169.4 (*C*OO); ir: (sodium chloride): 3420 (OH), 1744 (NC=O), 1735 (C=O), 1247 and 1081 (CO) cm^{-1}; ms: m/z 224, 206, 180; hplc Hypersil ODS C-18 (5μ), acetonitrile:water (2.81 g/l sodium perchlorate, *p*H = 3.00) (10:90), flow rate: 0.6 ml/minute, uv: 235 nm, retention time = 3.21 minutes, purity = 92%.

4-[2-[6-(3-Chlorophenyl)-2-hydroxy-2-methylperhydro-1,4-oxazine-4-yl]propyl]phenoxyethanoic Acid Hydrochloride (**4c1**).

Hydrolysis of the ester was carried out following the general method. A yellow oil was digested with acetone to give yellow needles (0.26 g, 32%), mp 103-104°; ^{1}H nmr (deuterioacetone): δ 1.25 (d, 3H), 1.47 and 1.50 (two singlets that correspond to the different stereoisomers, 3H), 2.73 (t, J = 11.6 Hz, 1H), 3.14 (t, J = 11.3 Hz, 1H), 3.30-3.75 (m, 5H), 4.63 (s, 2H), 4.00-5.00 (ws, 3H, -OH, -COOH, HCl), 5.61 (t, 1H), 6.84 (d, J = 8 Hz, 2H), 7.23 (d, J = 8 Hz, 2H), 7.40 (m, 4H); ^{13}C nmr (deuterioacetone): δ 13.1, 13.8 (*C*-C-N), 26.4, 26.6 (*C*-C-O), 36.8, 37.2 (*C*-C-N), 53.8, 54.0 (*C*-N), 55.0, 55.4 (*C*-N), 60.6, 60.7 (*C*-N), 64.8 (O-*C*-COO), 69.6, 69.8 (*C*-O), 93.8 (hemiacetal carbon), 114.1 to 156.2 (aromatic carbons), 170.4 (*C*OO); ir (potassium bromide): 3420 (OH), 2371 (NH^+), 1739 (C=O), 1208 and 1074 (CO) cm^{-1}; ms: m/z 254, 236, 210.

Anal. Calcd. for $C_{22}H_{27}Cl_2NO_5$: C, 57.89; H, 5.92; N, 3.07. Found: C, 57.98; H, 6.26; N, 2.82.

4-[2-[6-(3-Chlorophenyl)-2-hydroxy-2-phenylperhydro-1,4-oxazine-4-yl]propyl]phenoxyethanoic Acid Hydrochloride (**4d1**).

Hydrolysis of the ester was carried out following the general method. A yellow oil was obtained (0.45 g, 72%); ^{1}H nmr (deuterioacetone): δ 1.25 (d, 3H), 2.75 (m, 1H), 3.10-4.00 (m, 6H), 4.59 (s, 2H), 5.29 (m, 1H), 6.34 (ws, 2H, -OH, COOH), 6.80 (d, J = 8 Hz, 2H), 7.00-8.10 (m, 11H), 9.00 (ws, HCl); ^{13}C nmr (dimethyl sulfoxide): δ 11.2, 12.9, 14.5, 15.5 (*C*-C-N), 34.0, 35.2, 37.1, 38.0 (*C*-C-N), 50.5, 51.4, 52.0 (*C*-N), 52.1, 55.0, 55.5 (*C*-N), 63.2 (*C*-N), 64.4 (O-*C*-COO), 67.6, 67.7 (*C*-O), 94.5 (hemiacetal carbons), 114.0 to 156.4 (aromatic carbons) 168.9, 169.7 (*C*OO); ir (sodium chloride): 3424 (OH), 2550 (NH^+), 1737 (C=O), 1210 and 1078 (CO) cm^{-1}; ms: m/z 316, 298, 272, 193; hplc: Nucleosil 120 C-18 (5μ), acetonitrile:water (2.81 g/l sodium perchlorate, *p*H = 3.00) (25:75), flow rate: 0.5 ml/minute, uv: 240 nm, retention time = 4.20 minutes, purity = 72%.

2-[1-(4-Methylphenyl)ethylamino]-1-phenylethanol Hydrochloride (**5**).

Phenylethanolamine (6.85 g, 50.00 mmoles), triethylamine (21.4 ml, 154.04 mmoles), methyl 4-methylphenyl ketone (6.70 g, 50.00 mmoles) and methanol (60 ml) were added to a dry flask with septum and nitrogen bubbler, containing molecular sieves. Zinc iodide (7.98 g, 25.00 mmoles) in methanol (20 ml) was added *via* syringe. The reaction was stirred for 24 hours, quenched with a methanolic solution of sodium cyanoborohydride (9.45 g, 150.47 mmoles in 30 ml of methanol) and stirred for 24 hours. Part of the methanol was removed *in vacuo*. The residue was taken up in 2*N* sodium hydroxide (10 ml) and extracted with ethyl acetate (3 x 20 ml). The combined extracts were extracted with a 2*N* hydrochloric acid solution. The aqueous layer was basified and extracted with ethyl acetate (3 x 20 ml). The combined extracts were dried and evaporated *in vacuo*. An oil was obtained. It was purified by column chromatography

(silica gel, dichloromethane:methanol (1:99)). The oil was dissolved in ethanol, and ethyl ether saturated in hydrogen chloride (5 ml) was added, precipitating the product. It was recrystallized from acetone:ethyl ether:petroleum ether (8.33 g, 65%), mp 123-124°; ^{1}H nmr (deuterioacetone) (free base): δ 1.58 (d, J = 6.6 Hz, 3H), 2.27 (s, 3H), 2.70 (dd, 1H), 2.85 (dd, 1H), 4.10 (q, J = 6.6 Hz, 1H), 4.97 (t, 0.52H), 5.12 (m, 0.48H), 7.01-7.33 (m, 11H); ^{13}C nmr (deuterioacetone) (free base): δ 20.4 (*C*-Ar), 23.1, 23.5 (*C*-C-N), 55.0, 55.6 (*C*-N), 57.3, 58.1 (*C*-N), 71.4, 72.1 (*C*-O), 125.9 to 143.7 (aromatic carbons); ir (potassium bromide): 3350 (OH), 2770 (NH_2^+), 1378 (CH_3) cm^{-1}; ms: m/z 222, 148, 119.

Anal. Calcd. for $C_{17}H_{22}ClNO$: C, 69.98; H, 7.55; N, 4.80. Found: C, 69.75; H, 8.03; N, 4.73.

Methyl 4-[5-Phenyl-3-[1-(4-methylphenyl)ethyl]oxazolidine-2-yl]benzoate Hydrochloride (**6a**).

A mixture of 2-[1-(4-methylphenyl)ethylamino]-1-phenylethanol **5** (1.00 g, 3.92 mmoles), methyl 4-formylbenzoate (0.64 g, 3.90 mmoles), zinc iodide (catalytic quantity) and toluene (30 ml) was heated under reflux for 14 hours, using a Dean-Stark system. The organic layer was washed with brine (2 x 20 ml) and then dried. The solvent was evaporated to give an oil. The oil was chromatographed (silica gel, petroleum ether-ethyl ether (80:20)). Three fractions were obtained. After vacuum evaporation, an oil was obtained for each one. They were dissolved in ethanol, and ethanol saturated with hydrogen chloride (5 ml) was added. The solutions were evaporated *in vacuo*. The oils obtained were digested with petroleum ether:carbon tetrachloride. Fraction I (highest retardation factor) was obtained as an oil (0.28 g, 18%); ^{1}H nmr (deuterioacetone): δ 1.16, 1.23, 1.30, 1.45 (four doublets correspond to the different stereoisomers, 3H), 2.14, 2.18, 2.24, 2.26 (four singlets correspond to the different stereoisomers, 3H), 2.48 (t, 1H), 2.88 (t, 1H), 3.69 (m, 1H), 3.86 (s, 3H), 5.11 (m, 1H), 5.42, 5.49, 5.55 (three singlets correspond to the different stereoisomers), 6.90-8.15 (m, 13H); ir (sodium chloride): 2544 (NH^+), 1726 (C=O), 1379 (CH_3) cm^{-1}.

Fraction II (intermediate retardation factor) was obtained as a yellow solid (0.20 g, 13%), mp 74-76°; ^{1}H nmr (deuterioacetone) (free base): δ 1.31, 140 (two doublets correspond to the different stereoisomers, 3H), 2.24 (s, 3H), 2.48 (t, 1H), 2.72 (t, 1H), 3.71 (s, 1H), 3.81 (s, 3H), 3.96 (m, 1H), 4.62 (m, 1H), 7.00-7.25 (m, 9H), 7.45 (d, 2H), 7.92 (d, 2H); ^{13}C nmr (deuterioacetone) (free base): δ 13.6, 16.9 (*C*-C-N), 20.9 (*C*-Ar), 51.9 (*C*-OOC), 55.2, 55.4 (*C*-N), 58.4, 59.1 (*C*-N), 71.5 (*C*-O), 96.8 (O-*C*-N), 126.5 to 146.8 (aromatic carbons), 166.9 (*C*OO); ir (potassium bromide): 2611 (NH^+), 1724 (C=O), 1381 (CH_3) cm^{-1}; ms: m/z 148, 135, 119.

Anal. Calcd. for $C_{26}H_{28}ClNO_3 \cdot H_2O$: C, 68.50; H, 6.59; N, 3.07. Found: C, 68.81; H, 7.06; N, 2.71.

Fraction III (lowest retardation factor) was obtained as an oil (0.70 g, 45%); ^{1}H nmr (deuterioacetone) (free base): δ 1.31 (d, 3H), 2.25 (s, 3H), 2.58 (t, 1H), 2.69 (t, 1H), 3.83 (s, 3H), 3.97 (m, 1H), 4.71 (s, 1H), 4.80 (m, 1H), 7.07 (d, J = 7 Hz, 2H), 7.24 (m, 7H), 7.47 (d, J = 8 Hz, 2H), 7.98 (d, J = 8 Hz, 2H); ir (sodium chloride): 2588 (NH^+), 1723 (C=O), 1380 (CH_3) cm^{-1}; ms: m/z 296, 149, 119.

3-[1-(4-Methylphenyl)ethyl]-5-phenyloxazolidin-2-one (**6b**).

2-[1-(4-Methylphenyl)ethylamino]-1-phenylethanol **5** (0.70 g, 2.74 mmoles), *N,N'*-carbonyldiimidazole (0.47 g, 2.89 mmoles) and tetrahydrofuran (10 ml) were stirred at reflux for 24 hours. The solvent was evaporated. Ethyl acetate (50 ml) was added and the organic layer was washed successively with 1% hydrochloric acid (2 x 20 ml) and brine (2 x 20 ml). The organic layer was dried and the solvent was evaporated to give an oil. The oil was chromatographed (silica gel, dichloromethane:methanol (99:1)) and an oil was obtained (0.39 g, 50%); ^{1}H nmr (deuterioacetone): δ 1.48 (dd, 3H), 2.22 (s, 1.29H), 2.28 (s, 1.71H), 3.05 (t, 0.57H), 3.46 (t, 0.43H), 3.65 (t, 0.57H), 4.03 (t, 0.43H), 5.22 (m, 1H), 5.51 (dd, 1H), 7.16-7.46 (m, 9H); ^{13}C nmr (deuterioacetone): δ 16.5, 16.8 (*C*-C-N), 20.7, 20.7 (*C*-Ar), 47.9, 48.0 (*C*-N), 51.6, 51.8 (*C*-N), 74.6 (*C*-O), 125.9 to 139.9 (aromatic carbons), 157.2, 157.2 (N-*C*OO); ir (sodium chloride): 1747 (C=O), 1373 (CH_3), 1030 (CO) cm^{-1}; hplc: Spherisorb ODS 2 C-8 (5μ), methanol, flow rate: 0.5 ml/minute, refraction index, retention time = 3.38 minutes, purity = 99%.

4-[1-(4-Methylphenyl)ethyl]-2-methyl-6-phenylperhydro-1,4-oxazin-2-ol Hydrochloride (**6c**).

2-[1-(4-Methylphenyl)ethylamino]-1-phenylethanol **5** (1.00 g, 3.92 mmoles), chloroacetone (0.52 g, 5.62 mmoles), potassium bicarbonate (1.18 g, 11.78 mmoles), potassium iodide (0.17 g, 1.02 mmoles) and zinc iodide (catalytic quantity) were refluxed in acetone (35 ml), with nitrogen atmosphere, for 24 hours. The solvent was evaporated *in vacuo*. The residue was treated with brine (20 ml) and extracted with ethyl acetate (2 x 20 ml). The organic layer was dried and the solvent was evaporated. The residue was chromatographed (silica gel, dichloromethane:methanol (99:1)). The oil was dissolved in ethanol, and ethanol saturated with hydrogen chloride (5 ml) was added. The oil obtained was digested with petroleum ether:ethyl ether to obtain the hydrochloride as a brown solid (0.20 g, 14%), mp 117-118°; ^{1}H nmr (deuterioacetone): δ 1.05 (t, J = 6.8 Hz, 1.5H, CH_3 from ethanol), 1.32 (s, 3H), 1.82 (sc, 3H), 2.21 and 2.29 (two singlets that correspond to the different stereoisomers, 3H), 2.50-3.20 (m, 3.5H, OH from ethanol), 3.34 (q, J = 7.0 Hz, 1H, CH_2 from ethanol), 3.85 (m, 2H), 4.52 (m, 1H), 5.23 and 5.62 (two multiplets that correspond to the different steroisomers, 1H), 7.00-7.70 (m, 9H), 12.40 (ws, 1H, HCl); ^{13}C nmr (deuterioacetone): δ 11.3, 11.7, 15.1 (*C*-C-N^+), 17.0 (*C*-C-O, from ethanol), 20.7, 20.8 (*C*-Ar), 26.7 (*C*-C-O), 50.1, 54.8, 55.5 (*C*-N^+), 56.9, 59.0, 60.2 (*C*-N^+), 65.6 (*C*-O, from ethanol), 67.6, 68.4 (*C*-N^+), 69.0, 74.9 (*C*-O), 94.1 (hemiacetal carbon), 126.2 to 140.1 (aromatic carbons); ir (potassium bromide): 3414 and 3300 (OH), 2616 and 2343 (NH^+), 1384 (CH_3), 1081 (CO) cm^{-1}; ms: m/z 311 (M^+), 192, 176, 119, 91, 77.

Anal. Calcd. for $C_{20}H_{26}ClNO_2 \cdot 1/2EtOH \cdot 1/2H_2O$: C, 66.40; H, 7.91; N, 3.68. Found: C, 66.31; H, 7.86; N, 3.17.

4-[1-(4-Methylphenyl)ethyl]-2,6-diphenylperhydro-1,4-oxazin-2-ol Hydrochloride (**6d**).

In a flask with nitrogen atmosphere, 2-[1-(4-methylphenyl)-ethylamino]-1-phenylethanol **5** (0.40 g, 1.57 mmoles), chloromethyl phenyl ketone (0.21 g, 1.35 mmoles), potassium bicarbonate (0.41 g, 4.09 mmoles), potassium iodide (0.10 g, 0.60 mmoles) and acetone (10 ml) were introduced. The mixture was refluxed under nitrogen for 24 hours. The solution obtained was cooled and filtered. The solvent was evaporated. The residue was dissolved in absolute ethanol (5 ml), and ether saturated with hydrogen chloride (5 ml) was added. The residue was then cooled to 0° and stirred. A mixture of carbon tetrachloride and

petroleum ether was added to complete the precipitation of the hydrochloride. The solid that separated was then filtered and washed with petroleum ether (0.14 g, 23%), mp 69-70°; ^{1}H nmr (deuterioacetone): δ 1.94 (d, 3H), 2.33 (s, 3H), 2.90-4.10 (m, 4H), 4.71 (m, 1H), 5.50 (m, 1H), 6.90-7.90 (m, 14H), 10.20 (b, OH, HCl); ^{13}C nmr (deuterioacetone): δ 16.0, 16.5, 19.0, 19.4 (*C*-C-N), 20.4 (*C*-Ar), 53.3, 54.3, 54.7 (*C*-N), 58.1, 58.8, 59.5 (*C*-N), 67.8, 68.6 (*C*-N), 69.1 (*C*-O), 125.9 to 141.5 (aromatic carbons); ir (potassium bromide): 3283 (OH), 2742 (NH^+), 1385 (CH_3), 1064 (CO) cm^{-1}; ms: m/z 356, 148, 119.

Anal. Calcd. for $C_{25}H_{28}ClNO_2 \cdot 5/4H_2O$: C, 69.44; H, 7.06; N, 3.24. Found: C, 69.69; H, 6.76; N, 3.14.

4-[1-(Methylphenyl)ethyl]-6-phenylperhydro-1,4-oxazin-2-ol Hydrochloride (**6e**).

2-[1-(4-Methylphenyl)ethylamino]-1-phenylethanol **5** (1.00 g, 3.92 mmoles), triethylamine (1.7 ml, 12.23 mmoles), ethanedial 40% (0.65 ml, 4.30 mmoles), sodium cyanoborohydride (0.75 g, 11.94 mmoles) and methanol (9 ml) were added to a dry flask with septum and nitrogen bubbler, containing molecular sieves. The mixture was stirred for 24 hours, after which ethanedial 40% (0.65 ml, 4.30 mmoles) and zinc iodide (catalytic quantity) were added. The mixture was stirred for 3 days. Part of the methanol was removed *in vacuo*. The residue was taken up in 2*N* sodium hydroxide (10 ml) and extracted with ethyl acetate (3 x 20 ml). The combined extracts were extracted with 2*N* hydrochloride acid. The aqueous layer was basified and extracted with ethyl acetate (3 x 20 ml). The combined extracts were dried and evaporated *in vacuo*. The oil was purified by column chromatography (silica gel, dichloromethane:methanol (99.5:0.5)). The oil was dissolved in carbon tetrachloride, and ethanol saturated with hydrogen chloride (5 ml) was added. The solution was evaporated *in vacuo*. The solid obtained was digested with petroleum ether:ethyl ether. It was then filtered and washed with petroleum ether and carbon tetrachloride (0.76 g, 89%), mp 106-107°; ^{1}H nmr (deuterioacetone) (free base): δ 1.35 (d, J = 6.5 Hz, 3H), 1.87-2.09 (m, 2H), 2.29 (s, 3H), 2.75-3.22 (m, 2H), 3.41 (m, J = 6.5 Hz, 1H), 4.69 (dd, 1H), 5.14 (m, 2H), 7.10-7.42 (m, 9H); ^{13}C nmr (deuterioacetone) (free base): δ 18.7, 18.8 (*C*-C-N), 20.5 (*C*-Ar), 54.3, 55.5, 55.7, (*C*-N), 56.6, 56.8, 57.7 (*C*-N), 63.8, 63.9 (*C*-N), 70.2, 70.3, 75.8 (*C*-O), 90.5, 94.0, 94.1 (hemiacetal carbons), 125.8 to 140.8 (aromatic carbons); ir (potassium bromide): 3248 (OH), 2590 (NH^+), 1069 (CO) cm^{-1}; ms: m/z 297 (M^+), 178, 119.

Anal. Calcd. for $C_{19}H_{24}ClNO_2 \cdot 1/2H_2O$: C, 66.57; H, 7.30; N, 4.09. Found: C, 66.57; H, 7.78; N, 3.95.

4-[1-(4-Methylphenyl)ethyl]-6-phenylperhydro-1,4-oxazine-2,3-dione (**6f**).

2-[1-(4-Methylphenyl)ethylamino]-1-phenylethanol **5** (0.80 g, 3.13 mmoles), triethylamine (1.8 ml, 12.96 mmoles) and tetrahydrofuran (16 ml), were ice-cooled. Oxalyl chloride (0.44 g, 3.46 mmoles) in tetrahydrofuran (4 ml) was added during 15 minutes. The mixture was filtered and the solvent was evaporated. The residue was chromatographed (silica gel, dichloromethane:methanol (99:1)). A transparent oil (0.33 g, 34%); ^{1}H nmr (deuterioacetone): δ 1.72 (m, 3H), 2.29 (s, 3H), 3.75 (m, 2H), 4.22 (q, 1H), 5.54 (m, 1H), 7.10-7.40 (m, 9H); ^{13}C nmr (deuterioacetone): δ 20.09, 21.3 (*C*-C-N), 23.0 (*C*-Ar), 57.8, 58.4 (*C*-N), 66.4, 67.8 (*C*-N), 70.2, 77.3, 77.3 (*C*-O), 125.1 to 140.5 (aromatic carbons), 152.8, 153.1 (*C*ON), 156.6, 156.7 (*C*OO); ir (potassium bromide): 1773 (C=O lactone), 1686 (C=O lactam), 1069 (C-O) cm^{-1}; ms: m/z 190, 174, 119, 91, 77.

7-Methyl-4-[1-(4-methylphenyl)ethyl]-7-methoxy-2-phenyl-1,4-oxazepine (**6g**).

In a flask with a nitrogen atmosphere and molecular sieves 4Å, 2-[1-(4-methylphenyl)ethylamino]-1-phenylethanol **5** (1.27 g, 4.98 mmoles), butenone (0.70 g, 10.00 mmoles), *p*-toluensulfonic acid (catalytic quantity), toluene (5 ml) and methanol (5 ml) were introduced. The mixture was stirred at room temperature for 3 days. The solvent was evaporated. The residue was treated with 1*N* sodium hydroxide (10 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was dried and the solvent was evaporated. The residue was chromatographed (silica gel, dichloromethane:methanol (99.5:0.5)). A transparent oil (0.76 g, 57%); ^{1}H nmr (deuteriochloroform): δ 1.37 (m, 6H), 2.00 (m, 2H), 2.23 (m, 1H), 2.37 (s, 3H), 2.50 (m, 1H), 2.73 (m, 1H), 2.98 (m, 1H), 3.08 (s, 3H), 3.74 (q, 0.5H), 3.89 (q, 0.5H), 5.05 (m, 1H), 7.13-7.40 (m, 9H); ^{13}C nmr (deuteriochloroform): δ 16.2 (*C*-C-N), 19.3 (*C*-C-O), 20.0 (*C*-Ar), 23.8 (O-C-*C*-C-N), 41.6, 42.2 (*C*-N), 45.7, 46.7 (*C*-N), 48.6 (*C*-O), 61.4, 61.5, 62.5, 63.2 (*C*-N), 72.6, 73.1 (*C*-O), 102.4, 102.5 (acetal carbons), 126.1 to 142.1 (aromatic carbons); ir (potassium bromide): 2939 (CH_3, CH_2), 1381 (CH_3), 1063 (CO) cm^{-1}; ms: m/z 339 (M^+), 308, 218, 203, 119, 91, 77.

N-(4-Methoxyphenyl)chloroethanamide (**7a**).

p-Anisidine (2.10 g, 17.07 mmoles), triethylamine (2.4 ml, 17.27 mmoles) and toluene (30 ml) were mixed in a flask with magnetic stirring. The mixture was stirred well, and chloroacetyl chloride (1.38 ml, 17.32 mmoles) in toluene (30 ml) was added during 15 minutes. The organic layer was washed with brine and dried. The solvent was eliminated *in vacuo*. The solid was recrystallized from ethyl acetate/petroleum ether (0.85 g, 25%), mp 121-122°; ^{1}H nmr (deuterioacetone): δ 3.00 (s, NH), 3.80 (s, 3H), 4.24 (s, 2H), 6.93 (d, J = 8 Hz, 2H), 7.60 (d, J = 8 Hz, 2H); ir (potassium bromide): 3296 (NH), 1656 and 1544 (C=O), 1246 (CO), 830 cm^{-1}.

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.14; H, 5.01; N, 7.02. Found: C, 54.41; H, 5.14; N, 7.00.

N-(4-Methoxyphenyl)chloropropanamide (**7b**).

p-Anisidine (2.00 g, 16.26 mmoles), triethylamine (2.3 ml, 16.55 mmoles) and toluene (30 ml) were mixed in a flask with magnetic stirring. The mixture was stirred well, and 2-chloropropanoyl chloride (1.6 ml, 15.98 mmoles) in toluene (20 ml) was added during 15 minutes. The organic layer was washed with brine and dried. The solvent was eliminated *in vacuo*. The solid obtained was recrystallized from toluene (1.15 g, 34%), mp 106-107°; ^{1}H nmr (deuterioacetone): δ 1.71 (d, J = 6.55 Hz, 3H), 3.02 (s, NH), 3.81 (s, 3H), 4.66 (q, J = 6.50 Hz, 2H), 6.94 (d, J = 8 Hz, 2H), 7.63 (d, J = 8 Hz, 2H); ir (potassium bromide): 3258 (NH), 1660 and 1547 (C=O), 1249 (CO), 827 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}ClNO_2$: C, 56.21; H, 5.62; N, 6.56. Found: C, 56.23; H, 5.76; N, 6.40.

5-Phenyloxazolidine (**8**).

A solution of 2-amino-1-phenyl-1-ethanol (5.00 g, 36.49 mmoles) and formaldehyde 37% (4.6 ml, 61.38 mmoles) in tetrahydrofuran (50 ml) was stirred at reflux temperature for 2 hours and at room temperature for 19 hours. The tetrahydrofuran was eliminated, and the residue was dissolved in chloroform and

washed with water. The organic phase was evaporated until dry. The oil obtained was chromatographed (silica gel, dichloromethane:methanol (95:5)). A yellow oil (2.75 g, 51%); ^{1}H nmr (deuterioacetone): δ 2.85 (m, 1H), 3.65 (d, 1H), 3.68 (m, 1H), 4.68 (ws, 1H), 4.71 (d, 1H), 4.97 (dd, 1H), 7.41 (s, 5H); ^{13}C nmr (deuterioacetone): δ 57.8 (*C*-N), 75.2 (*C*-O), 84.7 (N-*C*-O), 124.6 to 142.7 (aromatic carbons); ir (sodium chloride): 3422 (NH), 1026 (CO), 758 and 701 cm^{-1}.

2-(2-Hydroxy-2-phenylethylamino)-*N*-(4-methoxyphenyl)-ethanamide (**9**).

A mixture of *N*-(4-methoxyphenyl)chloroethanamide **7a** (0.60 g, 3.02 mmoles), 2-amino-1-phenyl-1-ethanol (0.41 g, 2.99 mmoles), and triethylamine (0.5 ml, 3.59 mmoles) in ethanol (30 ml) was refluxed for 45 hours and then the solvent was evaporated. Dichloromethane (50 ml) was added and the organic layer was washed successively with a saturated potassium bicarbonate solution (2 x 20 ml). The organic layer was dried and the solvent was evaporated to give a solid. The solid was chromatographed (silica gel, dichloromethane:methanol (95:5)). Brown needles from chloroform/petroleum ether, mp 115-116°; ^{1}H nmr (deuterioacetone): δ 2.90 (m, 1H), 3.27 (b, OH, NH, CONH), 3.37 (s, 2H), 3.53 (m, 1H), 3.80 (s, 3H), 4.81 (m, 1H), 6.91 (d, J = 8 Hz, 2H), 7.00-7.60 (m, 7H); ir (potassium bromide): 3400 (OH, NH), 3297 (NH amide), 1656 and 1512 (C=O), 1236 (CO) cm^{-1}; ms: m/z 300 (M$^+$), 193, 165, 136, 107.

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 68.00; H, 6.67; N, 9.33. Found: C, 67.98; H, 6.93; N, 9.14.

N-(4-Methoxyphenyl)-2-(5-phenyloxazolidin-3-yl)ethanamide (**10a**).

A mixture of *N*-(4-methoxyphenyl)chloroethanamide **7a** (1.00 g, 5.03 mmoles), 5-phenyloxazolidine **8** (1.12 g, 7.51 mmoles), potassium carbonate (0.69 g, 4.99 mmoles) and potassium iodide (0.30 g, 1.80 mmoles) in ethanol (50 ml) was refluxed for 60 hours and then the solvent was evaporated. Ethyl acetate (50 ml) was added and the organic layer was washed successively with brine (2 x 20 ml). The organic layer was dried and the solvent was evaporated to give a solid. The solid was chromatographed (silica gel, dichloromethane:methanol (95:5)). Yellow needles were obtained from ethanol/petroleum ether (0.25 g, 16%), mp 105-106°; ^{1}H nmr (deuterioacetone): δ 3.00 (m, 2H), 3.58 (s, 2H), 3.87 (s, 3H), 4.58 (s, NH), 4.74 (d, J = 5.3 Hz, 1H), 4.78 (d, J = 5.3 Hz, 1H), 4.98 (t, 1H), 7.02 (d, J = 9 Hz, 2H), 7.31-7.66 (m, 7H); ^{13}C nmr coupled ^{1}H (deuterioacetone): δ 55.2 (q, *C*-O-Ar), 57.1 (t, *C*-N), 63.1 (t, N-*C*-CO), 71.5 (t, N-*C*-O), 72.1 (d, *C*-O), 114.3 to 156.9 (aromatic carbons), 169.6 (s, *C*OO); ir (potassium bromide): 3651 (NH), 1703 and 1514 (C=O), 1246 (CO), 828 cm^{-1}; ms: m/z 312 (M$^+$), 205, 165, 148, 107.

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.23; H, 6.41; N, 8.97. Found: C, 69.46; H, 6.75; N, 8.79.

N-(4-Methoxyphenyl)-2-(5-phenyloxazolidin-3-yl)propanamide (**10b**).

A mixture of 5-phenyloxazolidine **8** (1.00 g, 6.71 mmoles), *N*-(4-methoxyphenyl)chloropropanamide **7b** (0.70 g, 3.29 mmoles), potassium carbonate (0.65 g, 4.70 mmoles) and potassium iodide (0.30 g, 1.80 mmoles) in ethanol (30 ml) was refluxed for 46 hours and then the solvent was evaporated. Ethyl acetate (50 ml) was added and the organic layer was washed successively with brine (2 x 20 ml). The organic layer was dried and the solvent was evaporated to give an oil. The oil was chromatographed (silica gel, dichloromethane:methanol (99:1)) to give an orange oil (0.30 g, 16%); ^{1}H nmr (deuterioacetone): δ 1.41 two doublets that correspond to the different stereoisomers, J = 7.0 Hz, 3H), 2.58 (m, 1H), 3.45 (m, 1H), 3.69 (s, 1.2H), 3.75 (s, 1.8H), 4.28 (q, J = 6.8 Hz, 1H), 4.78 (d, 1H), 4.82 (d, 1H), 4.88 (m, 1H), 6.60-7.68 (m, 9H), 9.09 (b, 1H); ^{13}C nmr (deuterioacetone): δ 18.9, 20.7 (*C*-C-N), 55.0, 55.2 (*C*-N), 55.3 (*C*-O-Ar), 62.6 (N-*C*-CO), 68.3 (N-*C*-O), 72.6, 72.7 (*C*-O), 113.9 to 156.2 (aromatic carbons), 172.9, 175.4 (*C*OO); ir (sodium chloride): 3320 (NH), 1691 and 1514 (C=O), 1246 (CO), 831 cm^{-1}; ms: m/z 219, 148, 107.

N-(4-Methoxyphenyl)-2-[5-(3-chlorophenyl)oxazolidin-3-yl]-propanamide (**10c**).

A mixture of 5-(3-chlorophenyl)oxazolidine **2** (0.86 g, 4.68 mmoles), *N*-(4-methoxyphenyl)chloropropanamide **7b** (0.70 g, 3.29 mmoles), potassium carbonate (0.65 g, 4.70 mmoles) and potassium iodide (0.30 g, 1.80 mmoles) in ethanol (30 ml) was refluxed for 70 hours and then the solvent was evaporated. Ethyl acetate (50 ml) was added and the organic layer was washed successively with brine (2 x 20 ml). The organic layer was dried and the solvent was evaporated to give an oil. The oil was chromatographed (silica gel, dichloromethane:methanol (99:1)). To provide a brown oil (0.34 g, 20%); ^{1}H nmr (deuterioacetone): δ 1.23 (d, J = 6.7 Hz, 1.5H), 1.44 (d, J = 6.8 Hz, 1.5H), 2.72 (dd, 1H), 3.49 (m, 1H), 3.60 (s, 1.5H), 3.65 (s, 1.5H), 3.80 (q, J = 5.7 Hz, 1H), 4.55 (d, 1H), 4.60 (d, 1H), 4.86 (m, 1H), 6.57-7.53 (m, 8H), 9.20 (ws, 1H); ^{13}C nmr (deuterioacetone): δ 17.9, 18.5 (*C*-C-N), 54.8, 54.9 (*C*-N), 55.6 (*C*-O-Ar), 62.9, 63.4 (N-*C*-CO), 69.5, 70.0 (N-*C*-O), 73.8, 75.2 (*C*-O), 113.7 to 155.9 (aromatic carbons), 172.6 (*C*OO); ir (sodium chloride): 3337 (NH), 1669 and 1509 (C=O), 1243 (CO), 826 cm^{-1}; ms: m/z 328, 179, 123, 107.

5-[(3,4-Dihydro-2*H*-1-benzothiopyran-8-yl)oxymethyl]-3-(1,1-dimethylethyl)oxazolidin-2-one (**12a**).

Tertatolol **11** (1.00 g, 3.39 mmoles), *N,N'*-carbonyldiimidazole (0.51 g, 3.14 mmoles) and tetrahydrofuran (10 ml) were stirred at room temperature for 48 hours. The solvent was evaporated. Ethyl acetate (50 ml) was added, and the organic layer was washed successively with hydrogen chloride 1% (2 x 20 ml) and brine (2 x 20 ml). The organic layer was dried and the solvent was evaporated to give a solid. The solid was chromatographed (silica gel, dichloromethane:methanol (99:1)) and white needles were obtained from ethyl acetate/petroleum ether (0.50 g, 52%), mp 90-91°; ^{1}H nmr (deuterioacetone): δ 1.44 (s, 9H), 2.80-3.03 (m, 6H), 3.78 (dd, 1H), 3.87 (dd, 1H), 4.15 (dd, J = 4.2 Hz, 1H), 4.25 (dd, J = 3.7 Hz, 1H), 4.75 (m, J = 4.0 Hz, 1H), 6.73 (d, 1H), 6.81 (d, 1H), 6.96 (t, 1H); ^{13}C nmr (deuterioacetone): δ 22.9 (*C*-C-N), 26.8 (*C*-S), 27.2 (*C*-C-S), 30.6 (*C*-Ar), 45.1 (*C*-N), 53.4 (*C*-$(CH_3)_3$), 69.4 (*C*-O), 70.6 (*C*-O), 110.3 to 154.5 (aromatic carbons), 156.0 (N*C*OO); ir (potassium bromide): 1725 (C=O), 1266 and 1019 (CO) cm^{-1}; ms: m/z 321 (M$^+$), 306, 265, 166, 57.

Anal. Calcd. for $C_{17}H_{23}NO_3S$: C, 63.55; H, 7.17; N, 4.36. Found: C, 63.52; H, 7.48; N, 4.03.

6-[(3,4-Dihydro-2*H*-1-benzothiopyran-8-yl)oxymethyl]-4-(1,1-dimethylethyl)-2-hydroxy-2-methylperhydro-1,4-oxazine Hydrochloride (**12b**).

In a flask with a nitrogen atmosphere, **11** (0.80 g, 2.71 mmoles), chloroacetone (0.33 ml, 3.94 mmoles), potassium car-

bonate (0.99 g, 7.16 mmoles), potassium iodide (0.30 g, 1.80 mmoles), zinc iodide (catalytic quantity), molecular sieves and acetone (15 ml) were introduced. The mixture was refluxed under nitrogen for 24 hours. The solution obtained was cooled and filtered. The solvent was evaporated. The residue was chromatographed (silica gel, dichloromethane:methanol (99:1)). The oil was dissolved in petroleum ether-ethyl ether, and ethyl ether saturated with hydrogen chloride (5 ml) was added and digested with petroleum ether:ethyl ether. The hydrochloride precipitated as a beige solid (0.25 g, 24%), mp 109-111°; ^{1}H nmr (deuterioacetone) (free base): δ 1.03 (s, 9H), 1.09 (s, 1.26H), 1.13 (s, 1.74H), 1.97 (m, 2H), 2.69 (m, 2H), 2.85 (m, 4H), 3.20-3.70 (m, 2H), 3.70-4.10 (m, 4H), 6.58 (d, 1H), 6.67 (d, 1H), 6.80 (t, 1H); ^{13}C nmr (deuterioacetone) (free base): δ 22.2, 22.8 (*C*-C-N), 25.8, 26.2 (*C*-C-O), 26.6 (*C*-S), 27.4 (*C*-C-S), 31.6 (*C*-Ar), 53.0, 54.5 (*C*-N), 55.0, 55.2, 56.1 (*C*-N), 60.7, 62.9 (*C*-$(CH_3)_3$), 69.3, 69.7 (*C*-O), 70.5, 73.5 (*C*-O), 92.6 (hemiacetal carbon), 109.2 to 154.8 (aromatic carbons); ir (potassium bromide): 3406 (OH), 2600 (NH^+), 1256 and 1089 (CO) cm^{-1}; ms: m/z 351 (M^+), 336, 292, 166, 57.

Anal. Calcd. for $C_{19}H_{30}ClNO_3S$: C, 58.84; H, 7.74; N, 3.61. Found: C, 58.46; H, 8.11; N, 3.13.

6-[(3,4-Dihydro-2*H*-1-benzothiopyran-8-yl)oxymethyl]-4-(1,1-dimethylethyl)-2-hydroxy-2-phenylperhydro-1,4-oxazine Hydrochloride (**12c**).

In a flask with a nitrogen atmosphere, **11** (0.86 g, 2.91 mmoles), chloromethyl phenyl ketone (0.39 g, 2.52 mmoles), potassium bicarbonate (0.80 g, 8.00 mmoles), potassium iodide (0.18 g, 1.08 mmoles), zinc iodide (catalytic quantity), molecular sieves and acetone (50 ml) were introduced. The mixture was refluxed under nitrogen for 48 hours. The solution obtained was cooled and filtered. The solvent was evaporated. The residue was chromatographed (silica gel, dichloromethane:methanol (99:1)). The oil was dissolved in petroleum ether-ethyl ether, and ethyl ether saturated with hydrogen chloride (5 ml) was added. The solid obtained was digested with petroleum ether:ethyl ether. A yellow solid was obtained (0.18 g, 14%), mp 144-145°; ^{1}H nmr (deuterioacetone): δ 1.51 (s, 9H), 1.97 (m, 2H), 2.60-3.00 (m, 6H), 3.53 (m, 2H), 3.79 (m, 2H), 4.31 (s, 1H), 5.00 (m, 1H), 6.60-7.00 (m, 3H), 7.20-7.60 (m, 5H); ^{13}C nmr (deuterioacetone): δ 23.6 (*C*-C-N), 26.8 (*C*-S), 46.1 (*C*-N), 53.9 (*C*-N), 65.0 (*C*-$(CH_3)_3$), 66.0 (*C*-O), 69.6 (*C*-O), 95.0 (hemiacetal carbon), 110.5 to 154.7 (aromatic carbons); ir (sodium chloride) (free base): 3403 (OH), 1257 and 1085 (CO) cm^{-1}; ms: m/z 413 (M^+), 398, 356, 166, 57.

Anal. Calcd. for $C_{24}H_{32}ClNO_3S$: C, 64.07; H, 7.12; N, 3.11. Found: C, 63.90; H, 7.32; N, 2.82.

6-[(3,4-Dihydro-2*H*-1-benzothiopyran-8-yl)oxymethyl]-4-(1,1-dimethylethyl)-2-hydroxyperhydro-1,4-oxazine Hydrochloride (**12d**).

Tertatolol **11** (1.00 g, 3.39 mmoles), triethylamine (1.3 ml, 9.35 mmoles), ethanedial 40% (0.5 ml, 3.30 mmoles), sodium cyanoborohydride (0.58 g, 9.23 mmoles) and methanol (9 ml) were added to a dry flask with septum and nitrogen bubbler, containing molecular sieves. The mixture was stirred for 24 hours, after which ethanedial 40% (0.5 ml, 3.30 mmoles) and zinc iodide (catalytic quantity) were added. The mixture was stirred for 2 days. Part of the methanol was removed *in vacuo*. The residue was taken up in 2*N* sodium hydroxide (10 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was extracted with 2*N* hydrochloric acid. The aqueous layer was basified and extracted with ethyl acetate (3 x 20 ml). The combined extracts were dried and evaporated *in vacuo*. The yellow oil was purified by column chromatography (silica gel, chloroform:methanol (99.5:0.5)). The oil was dissolved in carbon tetrachloride, and ethanol saturated with hydrogen chloride (5 ml) was added. White needles were obtained (1.07 g, 96%), mp 181-182°; ^{1}H nmr (deuterioacetone) (free base): δ 1.04 (s, 9H), 1.98 (m, 2H), 2.29 (dd, J = 10 Hz, 2H), 2.74-2.90 (m, 6H), 3.14 (t, J = 9.5 Hz, 1H), 3.89 (d, J = 5.0 Hz, 2H), 4.07 (m, J = 4.6 Hz, 1H), 4.70 (ws, -OH), 4.80 (m, J = 8.0 Hz, 1H), 6.64 (t, 2H), 6.87 (t, 1H); ^{13}C nmr (deuterioacetone) (free base): δ 22.0 (*C*-C-N), 24.9 (*C*-S), 26.0 (*C*-C-S), 29.0 (*C*-Ar), 47.5, 48.7 (*C*-N), 50.8, 51.6 (*C*-N), 52.7, 52.8 (*C*-$(CH_3)_3$), 67.1, 69.4 (*C*-O), 72.1, 78.0 (*C*-O), 90.0, 93.9 (hemiacetal carbons), 109.0 to 153.8 (aromatic carbons); ir (potassium bromide): 3161 (OH), 2585 (NH^+), 1074 (CO) cm^{-1}; ms: m/z 337 (M^+), 322, 166, 57.

Anal. Calcd. for $C_{18}H_{28}ClNO_3S$: C, 57.83; H, 7.50; N, 3.75. Found: C, 57.82; H, 7.97; N, 3.46.

6-[(3,4-Dihydro-2*H*-1-benzothiopyran-8-yl)oxymethyl]-4-(1,1-dimethylethyl)perhydro-1,4-oxazin-3-one (**12e**).

Tertatolol **11** (1.00 g, 3.39 mmoles), triethylamine (0.5 ml, 3.59 mmoles), bromoacetyl bromide (0.3 ml, 3.37 mmoles) and tetrahydrofuran (10 ml) were mixed in a flask with magnetic stirring and then refluxed for 6 hours. Next, sodium (0.078 g, 3.40 mmoles) was added. The mixture was refluxed for 18 hours, methanol (10 ml) was added and the organic solution was evaporated *in vacuo*. The residue was taken up in water (10 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was dried and the solvent was evaporated to give an oil. The oil was chromatographed (silica gel, dichloromethane:methanol (99:1)). Beige needles were obtained from petroleum ether:ethyl ether (0.20 g, 18%), mp 94-95°; ^{1}H nmr (deuterioacetone): δ 1.42 (s, 9H), 1.97 (m, 2H), 2.73 (t, 2H), 2.91 (m, 2H), 3.40-3.65 (m, 2H), 3.94-4.14 (m, 5H), 6.64 (d, 1H), 6.70 (d, 1H), 6.85 (t, 1H); ^{13}C nmr (deuterioacetone): δ 22.7 (*C*-C-N), 26.7 (*C*-S), 27.6 (*C*-C-S), 29.6 (*C*-Ar), 45.2 (*C*-N), 57.2 (*C*-$(CH_3)_3$), 68.6 (O-*C*-CO), 69.2 (*C*-O), 72.7 (*C*-O), 110.0 to 154.3 (aromatic carbons), 167.2 (*C*ON); ir (potassium bromide): 1652 (C=O), 1256 and 1088 (CO) cm^{-1}; ms: m/z 335 (M^+), 320, 279, 166, 57.

Anal. Calcd. for $C_{18}H_{25}NO_3S$: C, 64.48; H, 7.46; N, 4.18. Found: C, 64.75; H, 7.93; N, 3.99.

6-[(3,4-Dihydro-2*H*-1-benzothiopyran-8-yl)oxymethyl]-4-(1,1-dimethylethyl)perhydro-1,4-oxazine-2,3-dione (**12f**).

Tertatolol **11** (0.80 g, 2.71 mmoles), triethylamine (1.4 ml, 10.07 mmoles) and tetrahydrofuran (12 ml) were mixed in a flask with magnetic stirring, on ice. The mixture was stirred well, and oxalyl chloride (0.33 g, 2.60 mmoles) in tetrahydrofuran (3 ml) was added for 10 minutes. The resulting solution was stirred for 30 minutes. Filtration yielded a clear organic solution which was evaporated *in vacuo*. The solid obtained was recrystallized with toluene:petroleum ether as white powder (0.70 g, 84%), mp 161-162°; ^{1}H nmr (deuterioacetone): δ 1.43 (s, 9H), 1.98 (m, 2H), 2.71-2.95 (m, 4H), 3.87-4.33 (m, 4H), 4.95 (m, 1H), 6.64 (d, 1H), 6.75 (d, 1H), 6.87 (t, 1H); ^{13}C nmr (deuterioacetone): δ 22.8 (CH_3), 26.8 (*C*-S), 27.5 (*C*-C-S), 29.0 (*C*-Ar), 43.8 (*C*-N), 58.6 (*C*-$(CH_3)_3$), 67.6 (*C*-O), 74.9 (*C*-O), 110.3 to 154.1 (aromatic carbons), 154.5 (*C*ON), 157.8 (*C*OO);

ir (potassium bromide): 1770 (C=O lactone), 1687 (C=O lactam), 1333 (lactam), 1188 (lactone) cm^{-1}; ms: m/z 349 (M^+), 293, 166, 57.

Anal. Calcd. for $C_{18}H_{23}NO_4S$: C, 61.89; H, 6.59; N, 4.01. Found: C, 61.98; H, 6.76; N, 3.98.

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