H_1-Antihistaminic Activity: Contraction of Isolated Ileum from Guinea Pigs Induced by Histamine (in Vitro). A study of the interaction with histamine was carried out with isolated ileum from guinea pigs according to the usual method. The segments (1 cm) of ileum were suspended in an organ bath containing Tyrode solution (ventilation, 32 °C). The contractile responses to histamine (5.4×10^{-7} mol/L) were measured with an isotonic transducer (TD-112S, Nihon Koden, Tokyo, Japan). Each test compound was added in the organ bath 5 min before the addition of histamine. IC_{50} values of the test compounds were calculated by the probit method.[9]

Histamine-Induced Mortality in Guinea Pigs (in Vivo). Histamine-induced mortality in guinea pigs was performed according to the method of Labelle and Tislow.[10] Groups of six to ten animals (250–350 g) were fasted for 20–24 h. Each test compound was administered orally, and 1 h later, histamine (1.1 mg/kg) was injected iv. The number of animals dying within 1 h after the injection of histamine was recorded. ED_{50} values of the test compounds were calculated by the probit method.[9]

Registry No. **3**, 1849-02-1; **4**, 80841-35-6; **5**, 101953-54-2; **6**, 101953-55-3; **7**, 101953-56-4; **8**, 101953-57-5; **9**, 72816-83-2; **10**, 24547-45-3; **11**, 43181-78-8; **12**, 101953-58-6; **13**, 87233-54-3; **14**, 101953-59-7; **15**, 87233-55-4; **16**, 87233-53-2; **17**, 101953-60-0; **18**, 87233-56-5; **19**, 95893-88-2; **20**, 95893-89-3; **22**, 57897-93-5; **23**, 101953-62-2; **24**, 55754-08-0; **25**, 101953-64-4; **27**, 101953-65-5; **27** (free base), 57897-97-9; **28**, 101953-67-7; **28** (free base), 101953-66-6; **29**, 101953-69-9; **29** (free base), 101953-68-8; **30**, 101953-71-3; **30** (free base), 101953-70-2; **31**, 101953-73-5; **31** (free base), 101953-72-4; **32**, 101953-75-7; **32** (free base), 101953-74-6; **33**, 101953-77-9; **33** (free base), 101953-76-8; **34**, 101953-78-0; **35**, 101953-80-4; **35** (free base), 101953-79-1; **36**, 101953-82-6; **36** (free base), 101953-81-5; **37**, 101953-84-8; **37** (free base), 101953-83-7; **38**, 101953-85-9; **38** (free base), 57897-96-8; **39**, 101953-87-1; **39** (free base), 101953-86-0; **40**, 101953-88-2; **41**, 101953-89-3; **42**, 101953-90-6; **43**, 101953-92-8; **43** (free base), 101953-91-7; **44**, 87233-66-7; **44** (free base), 87233-65-6; **45**, 101953-94-0; **45** (free base), 101953-93-9; **46**, 101953-96-2; **46** (free base), 101953-95-1; **47**, 101979-22-0; **47** (free base), 101954-34-1; **48**, 101953-98-4; **48** (free base), 101953-97-3; **49**, 101953-99-5; **50**, 101954-01-2; **50** (free base), 101954-00-1; **51**, 101954-02-3; **51** (free base), 87233-75-8; **52**, 87233-64-5; **52** (free base), 87233-63-4; **53**, 87233-60-1; **53** (free base), 87233-59-8; **54**, 101954-04-5; **54** (free base), 101954-03-4; **55**, 87233-78-1; **55** (free base), 87233-77-0; **56**, 101954-06-7; **56** (free base), 101954-05-6; **57**, 87233-70-3; **57** (free base), 87233-69-0; **58**, 87233-72-5; **58** (free base), 87233-71-4; **59**, 101954-08-9; **59** (free base), 101954-07-8; **60**, 101954-10-3; **60** (free base), 101954-09-0; **61**, 101954-12-5; **61** (free base), 101954-11-4; **62**, 101954-14-7; **62** (free base), 101954-13-6; **63**, 101954-15-8; **64**, 87233-80-5; **64** (free base), 87233-79-2; **65**, 101954-17-0; **65** (free base), 101954-16-9; **66**, 101954-19-2; **66** (free base), 101954-18-1; **67**, 87233-82-7; **67** (free base), 87233-81-6; **68**, 101954-21-6; **68** (free base), 101954-20-5; **69**, 87233-62-3; **69** (free base), 87233-61-2; **70**, 101954-23-8; **70** (free base), 101954-22-7; **71**, 101954-25-0; **71** (free base), 101954-24-9; **72**, 101954-27-2; **72** (free base), 101954-26-1; **73**, 101954-29-4; **73** (free base), 101954-28-3; **74**, 101954-31-8; **74** (free base), 101954-30-7; **75**, 87250-52-0; **75** (free base), 87233-83-8; **76**, 87233-68-9; **76** (free base), 87233-67-8; **77**, 87233-58-7; **77** (free base), 87233-57-6; **78**, 101954-33-0; **78** (free base), 101954-32-9; **79**, 87233-74-7; **79** (free base), 87233-73-6; $CH_3(CH_2)_2Br$, 106-94-5; $CH_3(CH_2)_3Cl$, 109-69-3; $CH_3(CH_2)_4Br$, 110-53-2; $CH_3(CH_2)_5Cl$, 544-10-5; $CH_3(CH_2)_6Br$, 629-04-9; $CH_3(CH_2)_9Br$, 112-29-8; $PhCH_2Cl$, 100-44-7; $Ph(CH_2)_2Br$, 103-63-9; $CH_2{=}CHOCH_2CH_2Cl$, 110-75-8; $CH_3(CH_2)_2O(CH_2)_2Br$, 64994-49-6; $CH_2{=}CHCH_2OCH_2CH_2Br$, 15424-04-1; $CH_3CH_2CH_2OCH_2CH_2Br$, 6550-99-8; $PhO(CH_2)_2Br$, 589-10-6; $HNCH_2CH_2CH_2N(CH_3)CH_2CH_2$, 4318-37-0; $Ph\text{-}NCH_2CH_2NH\text{-}CH_2CH_2$, 92-54-6; $Ph\text{-}CH_2\text{-}NCH_2CH_2NHCH_2CH_2$, 2759-28-6; $OHC\text{-}NCH_2CH_2NH\text{-}CH_2CH_2$, 7755-92-2; $HNCH_2CH_2CH_2NHCH_2CH_2$, 505-66-8; 2-chlorobenzimidazole, 4857-06-1; *N*-methylpiperazine, 109-01-3; 1-(2-ethoxyethyl)-2-benzimidazolone, 101953-61-1; 2-ethoxy ethylamine, 110-76-9; isoamyl chloride, 107-84-6; 1-phenyl-2-benzimidazolone, 14813-85-5; *o*-nitrochlorobenzene, 100-00-5; 1-bromo-2-chloroethane, 107-04-0.

(9) Finney, D. J. *Probit Analysis*; Cambridge University Press: London, 1964.
(10) Labelle, A.; Tislow, R. *J. Pharmacol. Exp. Ther.* **1955**, *113*, 72.

Two Stereoisomeric Imidazoline Derivatives: Synthesis and Optical and α_2-Adrenoceptor Activities

Jürgen Biedermann,* Alicia León-Lomelí, Harald O. Borbe, and Gerrit Prop

Departments of Chemical, Biochemical, and Pharmacological Research, A. Nattermann & Cie. GmbH, D-5000 Cologne 30, FRG. *Received July 31, 1985*

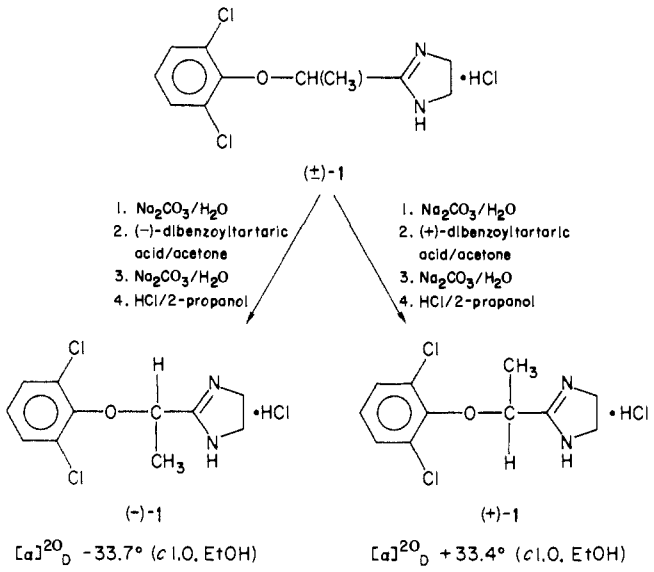
Two eight-step pathways for synthesizing the stereoisomeric compounds (-)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ("levlofexidine" hydrochloride; (-)-lofexidine hydrochloride) and (+)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ("dexlofexidine" hydrochloride; (+)-lofexidine hydrochloride) and the optical resolution of (±)-lofexidine are described. (-)-Lofexidine, a stereoselective α_2-adrenoceptor agonist, due to its center of asymmetry, is demonstrated to be a potent drug for the treatment of hypertension (doses 0.561 μg/kg) and to have the highest affinity and a concentration dependency for α_2-adrenoceptors in direct binding studies (0.36 nmol/L). (+)-Lofexidine is 10 times less potent.

Drugs with α_2-agonistic properties show a remarkable range of pharmacodynamic activities. This group of drugs comprises, in addition to clonidine and guanfacine representing the oldest and most completely investigated compounds, a series of newer compounds.[1] One of these drugs is another imidazoline compound, lofexidine hydrochloride[2-37] ((±)-**1**). The α_2-adrenoceptor agonists are clinically useful drugs for the treatment of hypertension. This blood pressure lowering effect is based on the stim-

(1) Timmermans, P. B. M. W. M.; van Zwieten, P. A. *Drugs Future* **1984**, *9*, 41.
(2) Ziegler, B.; Schneider, E.; AGNP 13. Nürnberger Symposium 1983 (5–8 Oct. 1983), Abstracts, 108.
(3) U.S. Patent 4382946; 4025639; 3966757; DE-PS 1795843.
(4) Timmermans, P. B. M. W. M.; van Kemenade, J. E.; Harms, Y. M.; Prop, G.; Graf, E.; van Zwieten, P. A. *Arch. Int. Pharmacodyn.* **1983**, *261*, 23.
(5) Fagan, T. C.; et al. *Br. J. Clin. Pharmacol.* **1982**, *13*, 405.
(6) Betzing, H.; Biedermann, J. *Arzneim.-Forsch./Drug. Res.* **1982**, *32*(II), 916.
(7) Wagener, H. H.; Genthe, H. *Arzneim.-Forsch./Drug Res.* **1982**, *32*, 918.
(8) Graf, E. *Arzneim.-Forsch./Drug Res.* **1982**, *32*, 923.

0022-2623/86/1829-1183$01.50/0

Scheme I



ulation of α_2-adrenoceptors in the brain. In addition, these drugs show such heterogeneous activities as antimigraine effects,[38] effects on menopausal flushing,[39] antidiarrheal activity,[21] and beneficial effects in states of opiate withdrawal.[2,33-35,40]

Table I. Blood Pressure Lowering Activity of Lofexidine and Its Enantiomers[a]

	stereochemical configuration		
dose, μg/kg	(−)	(±)	(+)
0.561	−22.6 ± 7.1		
1.0	−26.8 ± 4.1	−13.8 ± 1.9	−7.4 ± 7.4
3.16	−37.6 ± 3.6	−29.8 ± 4.2	−11.7 ± 10.7
5.61	−48.8 ± 6.6	−41.6 ± 8.6	
10.0	−54.2 ± 5.7	−53.0 ± 4.3	−10.6 ± 2.3

[a] Maximal decrease of mean arterial blood pressure (MAP) after intravenous injection in anesthetized normotensive rats.

Table II. Bradycardic Activity of Lofexidine and Its Enantiomers[a]

	stereochemical configuration		
dose, μg/kg	(−)	(±)	(+)
0.561	−52 ± 5		
1.0	−83 ± 6	−46 ± 5	−7 ± 4
3.16	−137 ± 12	−97 ± 12	−36 ± 1
5.61	−132 ± 9	−96 ± 5	
10.0	−138 ± 13	−134 ± 20	−61 ± 9

[a] Maximal decrease of heart rate after intravenous injection in anesthetized normotensive rats.

Lofexidine possesses an interesting and unique feature in that it has a center of asymmetry. All published research so far has been carried out with the racemic mixture. Recently a method has been developed for the synthesis of the enantiomers. An account of the pharmacological properties of the two stereochemical forms has been published for the first time recently.[41]

Our findings demonstrate that the cardiovascular activity is mainly seen with the (−) form compared with the (+) form, which is about 20 times weaker. In the present paper, the chemistry of the stereospecific synthesis of the two enantiomeric forms is described. The differing pharmacological activity is depicted in some biochemical and pharmacological test models.

Chemistry

Optical resolution of (±)-2-[1-(2,6-dichlorophenoxy)-ethyl]imidazoline hydrochloride ((±)-**1**, lofexidine hydrochloride) by using the classical methods of salt formation with (−)- and (+)-dibenzoyltartaric acid, as shown in Scheme I, yielded (−)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ((−)-**1**) and (+)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ((+)-**1**).

The preparation of both (−)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ((−)-**1**) and (+)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ((+)-**1**) was performed by starting with ethyl L-(−)-lactate ((−)-**2**) (Scheme II), a very inexpensive chemical.

In principle, the synthesis of (+)-**1** could also be undertaken, using ethyl D-(+)-lactate as starting material, in

(9) Graf, E.; Sieck, A.; Wenzl, H. *Arzneim.-Forsch./Drug Res.* **1982**, *32*, 931.
(10) Graf, E.; Doppelfeld, I. S.; Prop, G. *Arzneim.-Forsch./Drug Res.* **1982**, *32*, 941.
(11) Tsai, T. H.; Beitman, R. E.; Gibson, J. P.; Larson, E. J.; Friehe, H.; Fontaine, R. *Arzneim.-Forsch./Drug Res.* **1982**, *32*, 955.
(12) Tsai, T. H.; Beitman, R. E.; Gibson, J. P.; Larson, E. J. *Arzneim.-Forsch./Drug Res.* **1982**, *32*, 962.
(13) Friehe, H.; Fontaine, R.; Gibson, J. P.; Larson, E. J.; Sells, D. M. *Arzneim.-Forsch./Drug Res.* **1982**, *32*, 966.
(14) Midgleiy, I.; Chasseaud, L. F.; Taylor, T.; Darragh, A. *Arzneim.-Forsch./Drug. Res.* **1982**, *32*, 972.
(15) Aigner, A.; Schmidt, U. *Arzneim.-Forsch./Drug. Res.* **1982**, *32*, 976.
(16) Dollery, C. T.; Reid, J. L. *Arzneim.-Forsch./Drug. Res.* **1982**, *32*, 984.
(17) Beitman, R. E.; Kuzma, R. J.; McMahon, F. G.; Morledge, J.; Mroczek, W.; Rolf, C. N.; Tsai, T. H. *Arzneim.-Forsch./Drug. Res.* **1982**, *32*, 988.
(18) Timmermans, P. B. M. W. M.; de Jonge, A.; van Meel, J. C. A.; Slothorst Grisdijk, F. P.; Lam, E.; van Zwieten, P. A. *J. Med. Chem.* **1981**, *24*, 502.
(19) Garrett, B. N.; Kaplan, N. M. *J. Clin. Pharmacol.* **1981**, *21*, 173.
(20) Schultz, H. S.; Chretien, S. D.; Brewer, D. D.; Eltorai, M. I.; Weber, M. A. *J. Clin. Pharmacol.* **1981**, *21*, 65.
(21) Lal, H.; et al. *J. Clin. Pharmacol.* **1981**, *21*, 16.
(22) Wilkins, L. H.; et al. *Clin. Pharmacol. Ther.* **1981**, *30*, 752.
(23) Fouad, F. M.; Vidt, D. G.; Williams, H.; Tarazi, R. C.; Bravo, E. L. *Clin. Pharmacol. Ther.* **1981**, *29*, 498.
(24) St. John La Corte, W.; Jain, A. K.; Ryan, J. R.; McMahon, F. G. *Clin. Pharmacol. Ther.* **1981**, *29*, 259.
(25) Fouad, F. M.; et al. *Clin. Pharmacol. Ther.* **1980**, *27*, 254.
(26) Hague, D. E.; et al. *Clin. Pharmacol. Ther.* **1978**, *23*, 115.
(27) Burke, J. T.; et al. *Clin. Pharmacol. Ther.* **1977**, *21*, 99.
(28) Wilkins, L. H.; et al. *Clin. Res.* **1980**, *28*, 818A.
(29) Conti, J.; et al. *Clin. Res.* **1980**, *28*, 816A.
(30) Mauer, T.; Mehta, J.; Johnson, C.; Conti, C. R. *Clin. Res.* **1980**, *28*, 333A.
(31) Shearman, G. T.; et al. *Pharmacol. Biochem. Behav.* **1980**, *12*, 573.
(32) Lofexidine: Editorial Staff *Drugs Future* **1981**, *6*, 511; **1980**, *5*, 421; **1978**, *3*, 592.
(33) Gold, M. S.; et al. *Drug Alcohol Depend.* **1981**, *8*, 307.
(34) Washton, A. M.; Resnik, R. B.; Perzel, J. F.; Garwood, J. *Lancet* **1981**, *2*, 991.
(35) Gold, S. M.; Pottash, A. L. C.; Annitto, W. J.; Extein, I.; Kleber, H. D. *Lancet* **1981**, *2*, 992.
(36) Bloomfield, S. S.; et al. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1978**, *37*, 354.
(37) Velly, J. *J. Pharmacol. (Paris)* **1977**, *8*, 351.
(38) Brogden, R. N.; Pinder, R. M.; Sawyer, P. R.; Speight, T. M.; Avery, G. S. *Drugs* **1975**, *10*, 357.
(39) Clayden, J. R.; Bell, J. W.; Pollard, P. *Br. Med. J.* **1974**, *1*, 409.
(40) van der Laan, J. W.; van Veenendaal, W.; Voorthuis, P.; Weik, G.; Hillen, F. *Eur. J. Pharmacol.* **1985**, *107*, 367.
(41) Wilffert, B.; Mathy, M. J.; Batink, H. D.; de Jonge, A.; Thoolen, M. J. M. C.; Prop, G.; Graf, E.; Timmermans, P. B. M. W. M.; van Zwieten, P. A. *Arch. Int. Pharmacodyn.* **1985**, *273*, 18.

Scheme II

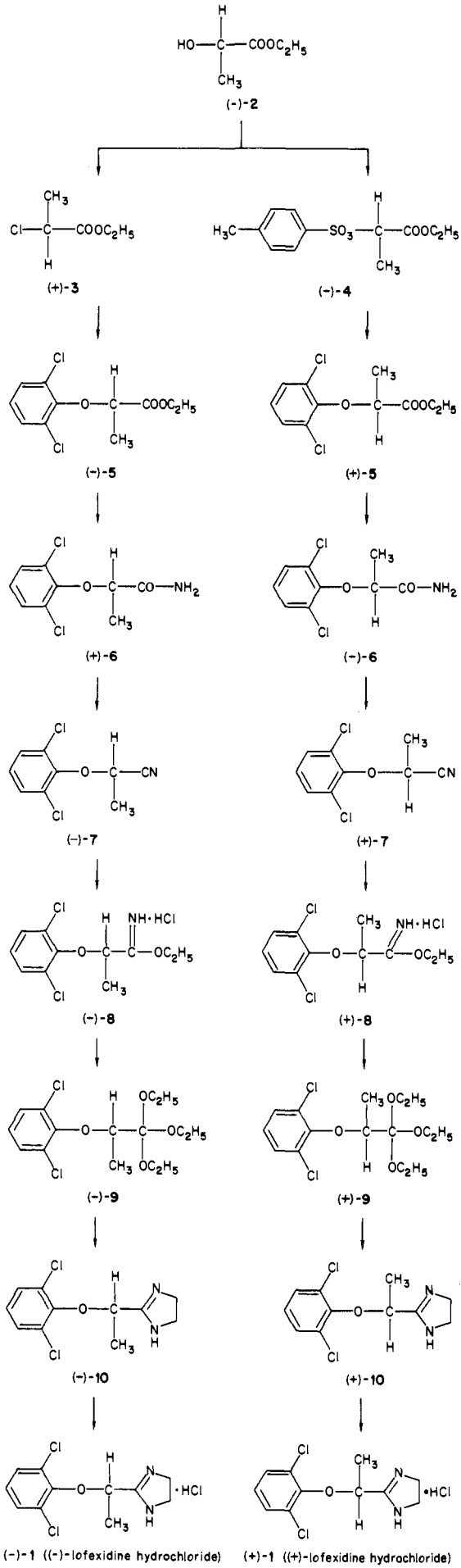


Table III. Half-Maximal Inhibition of Specific [^{3}H]Clonidine Binding[a]

displacer	IC_{50}, nmol/L
(±)-lofexidine	7.25 ± 0.7
(-)-lofexidine	3.60 ± 0.5
(+)-lofexidine	43.0 ± 7.0
phentolamine	37.5 ± 4.0
clonidine	17.3 ± 2.3

[a] The concentration of displacing agents that inhibited specific receptor binding by 50% (IC_{50}) was determined by log probit analysis, using eight different concentrations of the displacer. The data are means ± SE of four individual determinations each performed in triplicate.

analogy to the synthesis of (-)-**1**. However, in comparison to ethyl L-(-)-lactate, obtained by lactic fermentation, ethyl D-(+)-lactate is a very expensive starting material.

Step one in the preparation of (-)-**1** consisted in the transformation of the hydroxyl group into a chlorine leaving group by treatment of the neat ethyl L-(-)-lactate with thionyl chloride at reflux temperature, yielding (+)-**3**. This step proceeded with *inversion* of configuration.

In the case of the preparation of (+)-**1**, a tolylsulfonyl leaving group was chosen. Dissolving *p*-toluenesulfonyl chloride in ethyl L-(-)-lactate and treating this solution with triethylamine yields (-)-ethyl 2-[(*p*-tolylsulfonyl)-oxy]propionate ((-)-**4**) with *retention* of configuration.[42]

Steps two to eight were stereoisomeric for both compounds. Displacement of the chlorine group for (+)-**3** and the tolylsulfonyl group for (-)-**4** by using potassium 2,6-dichlorophenolate in 2-butanone proceeded in both cases with *inversion* of the configuration, yielding (-)-ethyl 2-(2,6-dichlorophenoxy)propionate ((-)-**5**) and (+)-ethyl 2-(2,6-dichlorophenoxy)propionate ((+)-**5**), respectively.

Steps three to eight consisted merely of transforming the ester group into an imidazoline heterocycle and had no influence on the configuration of the optically active carbon. Following ammonolysis of the ester (-)-**5** or (+)-**5** with a saturated solution of ammonia in ethanol at room temperature, (-)-2- and (+)-2-(2,6-dichlorophenoxy)-propionic acid amide, (+)-**6** and (-)-**6**, were formed. Subsequent dehydration of the amides (+)-**6** and (-)-**6** with a titanium tetrachloride–tetrahydrofuran complex in $CHCl_3$ at 0 °C and then at room temperature resulted in the expected (-)-2- and (+)-2-(2,6-dichlorophenoxy)-propionitrile ((-)-**7** and (+)-**7**). These nitriles were first transformed into the imidic acid ethyl ester hydrochlorides (-)-**8** and (+)-**8**, according to the method of Pinner[43] and then into the ortho esters (-)-**9** and (+)-**9**. The ortho esters were then cyclized with a solution of 1,2-diaminoethane in ethanol at -70 °C (then up to room temperature) and finally treated with HCl in 2-propanol to give (-)-**1** or (+)-**1**.

Biological Results and Discussion

The cardiovascular activity of (-)-lofexidine was very evident at doses as low as 0.561 μg/kg (Table I). This dose caused a lowering of the mean arterial blood pressure (22.6 ± 7.1 mmHg). The racemic mixture showed a weaker activity at 1.0 μg/kg, with a decrease of only 13.8 ± 1.9 mmHg. The blood pressure lowering effect of (+)-lofexidine was negligible at doses as high as 10.0 μg/kg. Considering the bradycardic results (Table II), the (-) form showed the strongest effect and the racemate was less

(42) Fiaud, J. C.; Horeau, A.; Kagan, H. B. *Stereochemistry Fundamentals and Methods*; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. 3, pp 4–9.

(43) Pinner, A. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 356. Dox, A. W. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 5.

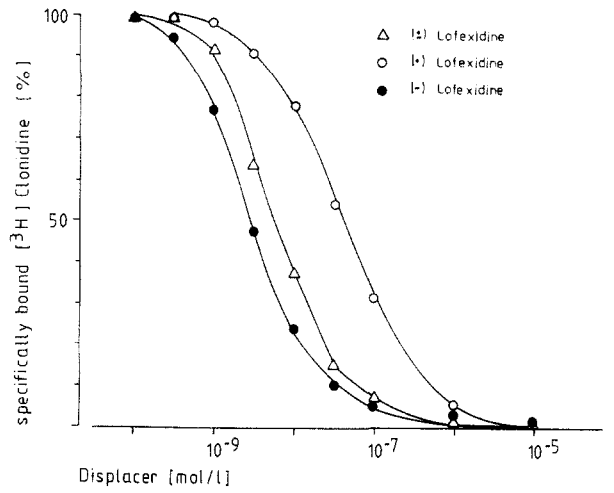


Figure 1. Competition of lofexidine for specific [^{3}H]clonidine binding. Specific ligand binding was assayed by the standard procedure described in the text. The points are the means of triplicate determinations of a typical experiment.

active while (+)-lofexidine only showed a very weak activity.

The results of direct binding studies on rat brain homogenate indicate that the occupation of α_2-adrenoceptors (labeled specifically with [^{3}H]clonidine) by lofexidine is concentration dependent (Figure 1). The binding of lofexidine and its stereoisomeric forms was found to be stereoselective (Table III).

(-)-Lofexidine showed the highest affinity with 3.6 nmol/L, whereas (+)-lofexidine was about 10-fold less potent. As expected, the racemic form of lofexidine was by half less active than (-)-lofexidine.

The stimulation of central α_2-adrenoceptors in the brain is responsible for the lowering of arterial blood pressure and heart rate after administration of clonidine and of other α_2-adrenergic compounds like, e.g., (±)-lofexidine.[44] This is evident from the cardiovascular data whereby (-)-lofexidine revealed a somewhat higher activity than the racemate; the (+) form in comparison showed a weak activity. A comparable order of potency has been obtained in the binding assay for α_2-adrenoceptors. On the other hand, in earlier experiments in pithed rats, a model where only the pressor response of compounds can be observed, it could be shown that (±)-lofexidine stimulates α_1- as well as α_2-adrenoceptors[41] and appears to be a nonselective α-adrenergic compound. The same authors found that there was no difference in the α_1/α_2-adrenoceptor selectivity between the two enantiomers.

Further investigation is in progress in order to characterize the different profiles of lofexidine (racemate) and (-)-lofexidine, especially concerning unwanted side effects (sedation, dry mouth).

Experimental Section

Pharmacological Methods. Male normotensive Wistar rats (200–350 g) were anesthetized with intraperitoneally injected sodium pentobarbitone (Nembutal; 75.0 mg/kg). The rats had been kept on a diet of laboratory pellets (Altromin) while tap water was allowed ad libitum.

The trachea was cannulated to allow unimpaired spontaneous breathing. The jugular vein and the carotid artery were cannulated with polyethylene catheters. Drug injections were carried out by way of the venous catheter. Arterial blood pressure was measured via a Statham P 23 D 6 pressure transducer connected to a Beckman Dynograph, type R, or to a Watanabe recorder WTR 281. Arterial blood pressure and pulse rate were recorded continuously. The animals were placed on a thermostated table, and rectal temperature was kept at ca. 37 °C. After a stabilization period of about 20 min, the animals were injected with the test solution (1 mL/kg). Each animal received only one injection.

Maximal falls in blood pressure and heart rate were measured. Drugs were dissolved in saline. Doses mentioned refer to the hydrochloride form of the drugs.

Receptor Binding Studies. Receptor binding studies were performed as described previously[45] with rat brain homogenates. Rats were decapitated, and the brains, without cerebella, were rapidly removed and stored at -20 °C until use. One frozen brain (1.5 g) was homogenized in 20 vol (w/v) of 0.05 mol/L Tris·HCl buffer (pH 7.7 at 25 °C) by using a glass homogenizer with a Teflon pestle and centrifuged twice at 48000*g* for 10 min at 4 °C. The supernatant was discarded and the resulting pellet was resuspended in 100 mL of ice-cold buffer. In the standard binding assay 1-mL aliquots of the crude membrane homogenate were incubated together with 20 μL of [^{3}H]clonidine (final concentration 2.5 nmol/L) and 50 μL of increasing concentrations of the displacers at 25 °C for 45 min. The incubation was terminated by filtration with Whatman GF/B glass fiber filters.

After washing the filters four times with 5 mL of ice-cold incubation buffer, the radioactivity was measured by liquid scintillation counting (LKB Rack Beta II) at a counting efficiency of 58%. Specific ligand binding was obtained by subtracting nonspecific binding—determined in the presence of an excess of unlabeled phentolamine—from total binding. IC_{50} values were determined by log-probit analysis by using eight increasing concentrations of the various displacers. Each determination, done in triplicate, was repeated four times and the mean value ± SE was calculated. [^{3}H]Clonidine (sp act. 777 GBq/mmol) was obtained from Amersham Buchler, Braunschweig, FRG.

Optical Resolution. (-)-2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline Hydrochloride ((-)-1). 10.0 g of (±)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline[6] dissolved in 350 mL of acetone was added to a stirring solution of 14.5 g of (-)-dibenzoyl-L-tartaric acid monohydrate, $[\alpha]^{20}_D$ -110° (*c* 1.0, EtOH), in 1500 mL of acetone at room temperature. After addition was completed, the reaction mixture was left without stirring 24 h and the resulting (-)-dibenzoyl-L-tartrate salt was collected by filtration (12.5 g, 52%); $[\alpha]^{20}_D$ -64° (*c* 1.0, EtOH). This salt was dissolved with a saturated sodium carbonate solution (50 mL) and the free base extracted with methylene chloride (3 × 100 mL). Drying and evaporation of the organic solvent left 6.5 g of the product, which was dissolved in 520 mL of acetone and added to a stirring solution of 9.4 g of (-)-dibenzoyl-L-tartaric acid monohydrate in 1950 mL of acetone. After 24 h, without stirring, the pure (-)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline (-)-dibenzoyl-L-tartrate salt crystallized (9.6 g, 62%); $[\alpha]^{20}_D$ -70.9° (*c* 1.0, EtOH). Further purification was carried out by recrystallization of the salt from hot ethanol (9.5 g in 180 mL) at 60 °C. The solution was left 24 h at room temperature, providing 5.9 g of the product; $[\alpha]^{20}_D$ -71.0° (*c* 1.0, EtOH). The second recrystallization (5.9 g in 90 mL ethanol) performed in the same manner as described above gave 3.9 g of (-)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline (-)-dibenzoyl-L-tartrate salt; $[\alpha]^{20}_D$ -75.9° (*c* 1.0, EtOH). (-)-Lofexidine free base was obtained by treatment of the salt with a saturated sodium carbonate solution (20 mL) and extraction with methylene chloride (3 × 100 mL); yield (1.6 g, 99%). (-)-2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ((-)-1) was obtained by dissolving the free base (-)-lofexidine in 2-propanol (3 mL) and adding at 5 °C an equimolar amount of a saturated HCl/2-propanol solution. The product was collected by filtration (1.4 g, 88%); mp 228–229 °C; $[\alpha]^{20}_D$ -33.7° (*c* 1.0, EtOH); $[\alpha]^{20}_{578}$ -35.5°; $[\alpha]^{20}_{546}$ -40.6°; $[\alpha]^{20}_{436}$ -73.0°; $[\alpha]^{20}_{365}$ -124.5°.

(+)-2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline Hydrochloride ((+)-1). The optical resolution of the pure isomer (+)-1 was carried out in a manner similar to that described for the (-)-lofexidine hydrochloride isomer, (-)-1. To 14.5 g of (+)-dibenzoyl-D-tartaric acid monohydrate, $[\alpha]^{20}_D$ +110° (*c* 1.0, EtOH), dissolved in 2 L of acetone was added a solution of 10.0

(44) Kobinger, W. *Rev. Physiol. Biochem. Pharmacol.* **1978**, *81*, 40.

(45) Borbe, H. O.; Zierenberg, O. *Pharmacopsychiatry* **1985**, *18*, 314.

g of (±)-lofexidine in 400 mL of acetone. (+)-Dibenzoyl-D-tartrate salt was obtained (12.8 g, 54%); $[\alpha]^{20}_D$ +65.6° (c 1.0, EtOH).

A solution of (+)-lofexidine free base (6.9 g), obtained as previously described for the (-)-lofexidine isomer, in 550 mL of acetone was added to a solution of (+)-dibenzoyl-D-tartric acid monohydrate (10.0 g in 2.2 L of acetone) to get the (+)-dibenzoyl-D-tartrate salt. (9.8 g, 63%); $[\alpha]^{20}_D$ +67.5° (c 1.0, EtOH).

This salt was twice recrystallized from hot ethanol (9.8 g in 250 mL) at 60 °C; yield 4.6 g; $[\alpha]^{20}_D$ +72.6° (c 1.0, EtOH). Second recrystallisation (4.6 g in 70 mL) at 60 °C; yield 2.9 g; $[\alpha]^{20}_D$ +77.8° (c 1.0, EtOH). The (+)-lofexidine free base and the (+)-lofexidine hydrochloride salt was worked up by methods analogous to those described above for the (-)-lofexidine, providing the (+)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline hydrochloride ((+)-1); yield 0.9 g (65%); mp 236–237 °C; $[\alpha]^{20}_D$ +33.4° (c 1.0, EtOH); $[\alpha]^{20}_{578}$ +35.2°; $[\alpha]^{20}_{546}$ +40.4; $[\alpha]^{20}_{436}$ +73.0°; $[\alpha]^{20}_{365}$ +125.0°.

Synthesis. All melting points were determined in an "Elektrothermal" melting point apparatus and are uncorrected. The IR spectra were measured on a Nicolet Instrument NIC-3600 grating infrared spectrophotometer in potassium bromide disks. The NMR spectra were measured with a Bruker WP 200 SY NMR spectrometer, ^{1}H-200 MHz in $CDCl_3$ or Me_2SO-d_6 solutions. The chemical shifts are expressed in parts per million (δ: ppm) from internal Me_4Si. The mass spectra were obtained on a Varian MAT 311 A mass spectrometer, data recording with a Finnigan-Incos System 2300. The optical activity was measured with a Perkin-Elmer 241 polarimeter. The spectral data for all new compounds were consistent with the assigned structures. Analyses were performed by Robert Glier "Mikro-Elementaranalysen Chemisch-physikalisches Labor", D-8721 Röthlein, FRG. Analytical results for the elements indicated were within ±0.4% of the theoretical values.

(+)-Ethyl 2-Chloropropionate ((+)-3). Thionyl chloride (264 g, 2.22 mol) was added to neat ethyl L-(-)-lactate ((-)-2; 250 g, 2.12 mol), $[\alpha]^{20}_D$ -11° (neat), and *N*,*N*-dimethylformamide (1.5 mL) at room temperature. The reaction mixture was boiled for 3.5 h until SO_2 evolution ceased. The product was then distilled (93 g, 32% yield); bp 143 °C; $[\alpha]^{20}_D$ +19.8° (neat); IR (KBr) 2980, 1740, 1380, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3 H), 1.65 (d, 3 H), 4.23 (q, 2 H), 4.38 (q, 1 H); MS, *m*/*e* 136 (6, M^+), 121 (2), 91 (45), 93 (14.6), 65 (67), 63 (100), 57 (53.6). Anal. ($C_5H_9ClO_2$) C, H, Cl.

(-)-Ethyl 2-(2,6-Dichlorophenoxy)propionate ((-)-5). A solution of 2,6-dichlorophenol (65.5 g, 0.40 mol) in 2-butanone (100 mL) was slowly added to a solution of potassium methoxide (38 g, 0.54 mol) in 2-butanone (200 mL) and stirred for 1 h at 40 °C. (+)-Ethyl 2-chloropropionate (76 g, 0.56 mol) was added dropwise to the stirred mixture at 70 °C. After 48 h the refluxing mixture was evaporated in vacuo, and the residue was diluted with water (200 mL) and was extracted into toluene (5 × 100 mL). The organic layers were washed with NaOH (5%) (1 × 50 mL), extracted with ethyl acetate (3 × 100 mL), washed with water, and dried and evaporated in vacuo. Distillation of the residue gave the product (60 g, 57%); bp 115–117 °C (0.3 mm); $[\alpha]^{20}_D$ -37.1° (neat); IR (KBr) 2986, 1745, 1565, 1447, 1247, 1204, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H), 1.63 (d, 3 H), 4.25 (q, 2 H), 4.83 (q, 1 H), 6.95–7.32 (m, 3 H, arom); MS, *m*/*e* 262 (22.6, M^+), 264 (15), 227 (11.3), 229 (3.5), 189 (60), 190 (39.9), 162 (100), 164 (64.3), 101 (31), 73 (49.4). Anal. ($C_{11}H_{12}Cl_2O_3$) C, H, Cl.

(+)-2-(2,6-Dichlorophenoxy)propionamide ((+)-6). A solution of (-)-ethyl 2-(2,6-dichlorophenoxy)propionate (60 g, 0.23 mol) in ethanol (150 mL) was saturated with a stream of NH_3 at room temperature (24 h). The amide was collected by filtration, washed with cold ethanol, and dried (41 g, 77%); mp 193 °C; $[\alpha]^{20}_D$ +20.1° (c 1.0, acetone); IR (KBr) 3409, 3176, 1633, 1451, 1444, 1252, 778 cm^{-1}; ^{1}H NMR (CD_3OD–$CDCl_3$) δ 1.53 (d, 3 H), 2.4 (br s, NH_2), 4.95 (q, 1 H), 6.9–7.4 (m, 3 H, arom); MS, *m*/*e* 233 (0.89, M^+), 235 (0.64), 198 (67.5), 200 (21), 189 (39), 191 (24.7), 162 (41.6), 164 (26), 72 (100), 44 (93.1). Anal. ($C_9H_9Cl_2NO_2$) C, H, N.

(-)-2-(2,6-Dichlorophenoxy)propionitrile ((-)-7). Titanium tetrachloride (16.3 g, 83 mmol) was slowly added to ethanol-free chloroform (250 mL) and tetrahydrofuran (7 mL) at 0 °C. After the addition, (+)-2-(2,6-dichlorophenoxy)propionamide (10 g, 43 mmol) was introduced. Then *N*-methylmorpholine (17.3 g, 170 mmol) was added dropwise to the cooled mixture, and upon completion, the reaction was left for 24 h at room temperature. A 120-mL sample of a saturated aqueous sodium chloride solution was added to the cooled reaction mixture and extracted with chloroform (3 × 100 mL). Drying and evaporation of the organic solvent left a residual oil. Distillation of the residue gave (-)-2-(2,6-dichlorophenoxy)propionitrile (7.0 g, 76%); bp 85 °C (0.2 mm); $[\alpha]^{20}_D$ -76.6° (neat); IR (KBr) 2995, 1568, 1445, 1241, 784 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.77 (d, 3 H), 5.0 (q, 1 H), 6.85–7.31 (m, 3 H, arom); MS, *m*/*e* 215 (39, M^+), 217 (28.8), 180 (5), 162 (100), 164 (74), 133 (35.7), 134 (24.8), 126 (14), 63 (31.6). Anal. ($C_9H_7Cl_2NO$) C, H, N.

(-)-2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline ((-)-10). A cooled solution of (-)-2-(2,6-dichlorophenoxy)propionitrile (20 g, 93 mmol) in dry chloroform (50 mL) and ethanol (4.3 g, 92 mmol) was saturated with a stream of HCl and the mixture was stirred for another 18 h at room temperature. The precipitated imino ester hydrochloride (-)-8 was collected by filtration and washed with cold chloroform. The product was redissolved in ethanol (20 mL) and stirred for 20 min to obtain the ortho ester (-)-9. After removal of the ammonium chloride, the clear solution was added dropwise to a stirred solution of ethylenediamine (6.0 g, 0.1 mol) in ethanol (100 mL) at -70 °C. The reaction mixture was allowed to reach room temperature. The solvent was evaporated in vacuo at room temperature and the product dried to give (16 g, 67%); mp 127–128 °C; $[\alpha]^{20}_D$ -90.0° (c 1.0, EtOH); $[\alpha]^{20}_{578}$ -94.0°; $[\alpha]^{20}_{546}$ -107.2°; $[\alpha]^{20}_{436}$ -188.5°; $[\alpha]^{20}_{365}$ -311.3°.

(-)-2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline Hydrochloride ((-)-1). To a cooled solution of (-)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline (4.0 g, 15 mmol) in 2-propanol (20 mL) was added dropwise an equivalent amount of HCl/2-propanol solution. The precipitated product was collected by filtration (3.3 g, 72%); mp 228–229 °C; $[\alpha]^{20}_D$ -41.0° (c 1.0, EtOH); $[\alpha]^{20}_{578}$ -42.9°; $[\alpha]^{20}_{546}$ -49.1°; $[\alpha]^{20}_{436}$ -88.3°; $[\alpha]^{20}_{365}$ -150.3°; IR (KBr) 3057, 2929, 2912, 2885, 1615, 1444, 1244, 1228, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83 (d, 3 H, ^3J = 6.84 Hz), 4.06 (s, 4 H, imidazoline methylene), 5.48 (q, 1 H, ^3J = 6.84 Hz), 7.1–7.4 (m, 3 H, arom; A_2B system, δ_A = 7.35, δ_B = 7.10, $^3J_{AB}$ = 8.2 Hz), 11.06 (s, 2 N^+–H); MS, *m*/*e* 258 (2.4, M^+), 260 (1.3), 243 (100), 245 (74.4), 247 (9.0), 223 (72.4), 225 (17.2), 97 (29.6), 67 (55.9), 36 (56). Anal. ($C_{11}H_{12}Cl_2N_2O$·HCl) C, H, Cl, N.

(-)-Ethyl 2-[(*p*-tolylsulfonyl)oxy]propionate ((-)-4). *p*-Toluenesulfonyl chloride (612 g, 3.21 mol) was dissolved at 40 °C with ethyl L-(-)-lactate (2.0 L). Triethylamine (323 g, 3.19 mol) was added dropwise to the mixture at room temperature and stirred for another 9 h. After removal by filtration of the triethylamine hydrochloride, the remaining ethyl L-(-)-lactate was distilled, bp 20 °C (0.3 mm). The residual oil was diluted with aqueous Na_2CO_3 (100 mL) and extracted with methylene chloride (3 × 100 mL), washed with water, dried, and evaporated in vacuo. The product was distilled (667 g, 70%), bp 146–147 °C (1.0 mm); $[\alpha]^{30}_D$-51.0° (neat); IR (KBr) 2987, 1755, 1369, 1206, 1190, 1178, 1082, 557; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3 H), 1.49 (d, 3 H), 2.44 (s, 3 H), 4.11 (q, 2 H), 4.92 (q, 1 H), 7.03–7.87 (m, 3 H, arom); MS, *m*/*e* 272 (4.8, M^+), 199 (32.3), 155 (100), 91 (71), 65 (17.5). Anal. ($C_{12}H_{16}O_5S$) C, H, S; C: calcd, 52.95; found, 52.06.

(+)-Ethyl 2-(2,6-Dichlorophenoxy)propionate ((+)-5). A solution of 2,6-dichlorophenol (84 g, 0.32 mol) in 2-butanone (200 mL) was portionwise added to a solution of potassium methoxide (46 g, 0.64 mol) in 2-butanone (150 mL) and stirred for 1 h at 40 °C. (-)-Ethyl 2-[(*p*-tolylsulfonyl)oxy]propionate (196 g, 0.72 mol) in 2-butanone (50 mL) was added dropwise to the stirred mixture at 70 °C. The reaction was stirred for 20 h. After the mixture was cooled, the tosylate salt was filtered and the residue diluted with 100 mL of aqueous sodium carbonate (5%) and extracted into toluene (2 × 100 mL). The organic layers were washed with water, dried, and evaporated in vacuo. Distillation of the residue yielded the product (105 g, 77%): bp 118–120 °C (0.35 mm); $[\alpha]^{20}_D$ +35.9° (neat); IR (KBr) 2985, 1744, 1585, 1447, 1247, 1201, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3 H), 1.62 (d, 3 H), 4.22 (q, 2 H), 4.83 (q, 1 H), 6.94–7.33 (m, 3 H, arom); MS, *m*/*e* 262 (21.8, M^+), 264 (14.3), 227 (8.9), 229 (2.5), 189 (77.8), 191 (34.9), 162 (100), 164 (79.6), 101 (56.2), 73 (81.3). Anal. ($C_{11}H_{12}Cl_2O_3$) C, H, Cl.

(-)-2-(2,6-Dichlorophenoxy)propionamide ((-)-6). (+)-Ethyl 2-(2,6-dichlorophenoxy)propionate dissolved in ethanol (50 mL) and aqueous ammoniacal solution (33%, 100 mL) was stirred for 48 h at room temperature. The product was filtered and washed with ethanol (34.4 g, 73%); mp 189 °C; $[\alpha]^{20}_D$ -19.9° (c 1.0,

acetone); IR (KBr) 3409, 3182, 1635, 1452, 1445, 779 cm^{-1}; ^1H NMR (DMF) δ 1.45 (d, 3 H), 4.78 (q, 1 H), 7.2–7.58 (m, 3 H, arom, 2 H–NH_2); MS, *m/e* 233 (0.23, M^+), 198 (33.7), 200 (11.4), 189 (22.2), 191 (14.6), 162 (28.3), 164 (17.5), 72 (70.4), 44 (100). Anal. ($C_9H_9Cl_2NO_2$) C, H, N.

(+)-2-(2,6-Dichlorophenoxy)propionitrile ((+)-7). Titanium tetrachloride (55 g, 0.29 mol) was slowly added to chloroform (850 mL) and tetrahydrofuran (25 mL) at 0 °C. After the addition was completed, (-)-2-(2,6-dichlorophenoxy)propionamide (34 g, 0.15 mol) was introduced and *N*-methylmorpholine (59 g, 0.58 mol) was added dropwise to the cooled mixture. The reaction was allowed to react 12 h at room temperature and then poured portionwise into 500 g of ice and extracted with chloroform (3 × 100 mL). Drying and evaporation of the organic phase left a residual oil, which was distilled, giving the product (149.3 g, 84%); bp 86 °C (0.15 mm); $[\alpha]^{20}_D$ +77.2° (neat); IR (KBr) 2998, 1567, 1445, 1241, 784 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (d, 3 H), 5.09 (q, 1 H), 7.05–7.36 (m, 3 H, arom); MS, *m/e* 215 (28.6), 217 (16.9), 162 (100), 164 (63.1), 133 (44.8), 135 (30.4), 73 (32.2), 75 (16.5), 63 (47.7), 126 (13.4). Anal. ($C_9H_7Cl_2NO$) C, H, N.

(+)-2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline ((+)-10). A cooled solution of (+)-2-(2,6-dichlorophenoxy)-propionitrile (20 g, 90.0 mmol) in dry chloroform (50 mL) and ethanol (4.5 g, 97.0 mmol) was saturated with a stream of HCl (gas). The reaction was stirred for 36 h at 0 °C. The organic phase was evaporated in vacuo at 10 °C and then the imino ester hydrochloride (+)-8 was precipitated with dry diethyl ether and collected by filtration. The product was redissolved in cool ethanol (50 mL) and stirred for 20 min to obtain the ortho ester (+)-9. The ammonium chloride was filtered and the clear solution was added dropwise to a stirred solution of ethylene diamine (6.0 g, 0.1 mol) in ethanol (100 mL) at −70 °C. The reaction mixture was allowed to reach room temperature and the product dried to give (9.7 g, 40%); mp 125–126 °C; $[\alpha]^{20}_D$ +73.7° (*c* 1.0, EtOH); $[\alpha]^{20}_{578}$ +76.89°; $[\alpha]^{20}_{546}$ +88.0°; $[\alpha]^{20}_{436}$ +162.1°; $[\alpha]^{20}_{365}$ +256.8°.

(+)-2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline Hydrochloride ((+)-1). To a cooled solution of (+)-2-[1-(2,6-dichlorophenoxy)ethyl]-2-imidazoline (9.7 g, 38.0 mmol) in 2-propanol (30 mL) was added dropwise an equivalent amount of HCl/2-propanol solution. A small amount of precipitated product was collected by filtration, $[\alpha]^{20}_D$ +6.19°. From the filtrate the main product was precipitated with diethyl ether (dry) and collected by filtration (6.0 g, 54%); mp 236–237 °C; $[\alpha]^{20}_D$ +37.9° (*c* 1.0, EtOH); $[\alpha]^{20}_{578}$ +39.7°; $[\alpha]^{20}_{546}$ +45.6°; $[\alpha]^{20}_{436}$ +82.5°; $[\alpha]^{20}_{365}$ +140.4°; IR (KBr) 3053, 2913, 2888, 1616, 1445, 1243, 783 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (d, 3 H, ^3J = 6.84 Hz), 4.06 (s, 4 H), 5.48 (q, 1 H, ^3J = 6.8 Hz), 7.1–7.4 (m, 3 H, arom; A_2B system, δ_A = 7.35, δ_B = 7.10, $^3J_{AB}$ = 8.2 Hz), 11.0 (s, 2 N^+–H); MS, *m/e* 258 (2.2, M^+), 260 (1.2), 243 (100), 245 (73.3), 247 (8.5), 223 (70.4), 225 (16.9), 97 (27.9), 67 (49.7), 36 (47.1). Anal. ($C_{11}H_{12}Cl_2N_2O$·HCl) C, H, Cl, N.

Acknowledgment. We acknowledge the expert technical assistance of Ingeborg Zube, Marion Steinmetz, Monika Speicher, and Heike Lange.

Registry No. (-)-1, 87038-06-0; (+)-1, 87858-98-8; (-)-2, 687-47-8; (+)-3, 42411-39-2; (-)-4, 57057-80-4; (-)-5, 86981-78-4; (+)-5, 87789-40-0; (+)-6, 86981-80-8; (-)-6, 87789-42-2; (-)-7, 86981-81-9; (+)-7, 87789-43-3; (-)-8, 101934-13-8; (+)-8, 101934-15-0; (-)-9, 101934-14-9; (+)-9, 101934-16-1; (-)-10, 81447-78-1; (+)-10, 81447-79-2; (±)-10, 73372-53-9; (-)-10·(-)-dibenzoyl-L-tartrate, 102044-00-8; (+)-10·(+)-dibenzoyl-D-tartrate, 102044-01-9; 2,6-dichlorophenol, 87-65-0; titanium tetrachloride, 7550-45-0; ethanediamine, 107-15-3.