cinamide (0.6 g) was suspended in 10 ml of trifluoroethanol and HBr was bubbled through for 30 min. The clear solution was kept for another hour at room temperature. The solvent was evaporated and the residue was washed with ether three times. The dried residue was dissolved in 6 ml of DMF and the pH was adjusted to 8 with triethylamine. *p*-Nitrophenyl β-benzylmercaptoisovalerate (0.35 g) was added and the solution was stirred for 4 days at room temperature. The semisolid mixture was treated successively with 80 ml of ethyl acetate, 40 ml of ethanol, and 40 ml of ethyl acetate and finally washed on the filter with 40 ml of ethyl acetate; 0.51 g. This material was used to prepare the analog. For analytical purposes the substance was reprecipitated from DMF–ethyl acetate and from THF–water; mp 234–237°, $[\alpha]^{20}D$ −48.5° (*c* 1, DMF).

Anal. Calcd for $C_{39}H_{53}N_{11}O_{12}S_2$: C, 58.9; H, 6.96; N, 12.8. Found: C, 58.7; H, 7.01; N, 12.6.

1-Deaminopenicillamine-oxytocin (1-β-Mercaptoisovaleric Acid-oxytocin).—β-Benzylmercaptoisovaleryl-L-tyrosyl-D-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (0.23 g) was dissolved in 50 ml of anhydrous liquid ammonia and reduced with sodium until the blue color lasted for a few seconds. The ammonia was removed by evaporation and lyophilization. The resulting white residue was dissolved in 230 ml of deaerated water, the pH was adjusted to 6.8 with acetic acid, and the theoretical amount of a 0.01 *N* potassium ferricyanide solution (38 ml) was added. The solution was deionized by passage through a column containing the ion-exchange resin [Rexyn CG (8) Cl] in the chloride form. The filtrate was concentrated to 50 ml, placed in the first five tubes of a countercurrent distribution machine, and subjected to 400 transfers in the solvent system 0.5% aqueous acetic acid (containing 0.1% pyridine)–1-butanol–benzene (5:3:2). A main peak with a *K* value of 2 was obtained as determined by the Folin-Lowry color values. Concentration and lyophilization of the fractions from the central part of the peak yielded 78 mg of 1-deaminopenicillamine-oxytocin with an optical rotation of $[\alpha]^{20}D$ −53.6° (*c* 0.5, 1 *N* acetic acid).

A small amount of this compound was subjected to gel filtration on Sephadex G-25 in the solvent 0.2 *N* acetic acid. A single peak emerged at the position of oxytocin. On paper chromatography the compound showed only one spot. For analysis a sample was dried (P_2O_5) at 100° *in vacuo* and a loss in weight of 6.5% was observed.

Anal. Calcd for $C_{43}H_{69}N_{11}O_{12}S_2$: C, 53.0; H, 6.82; N, 15.1. Found: C, 52.9; H, 6.92; N, 14.9.

Acknowledgments.—We wish to thank Dr. W. Y. Chan for the pharmacological studies on the compounds reported herein. These studies will be reported in greater detail elsewhere. We also wish to thank Mr. Joseph Albert for the elemental microanalyses.

Relationship between Configuration and Adrenergic β-Receptor Blocking Activity of Optical Isomers of 1-(4-Nitrophenyl)-2-isopropylaminoethanol (INPEA)

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1-(4-Nitrophenyl)-2-isopropylaminoethanol (INPEA), a highly specific adrenergic β-receptor, inhibitor, has been resolved into its optically active isomers. Pharmacologically it has been shown that only the levorotatory isomer displays β-receptor blocking activity. The optically pure dextrorotatory isomer was found to be completely inactive even at very high doses. The absolute D configuration of the active isomer was chemically determined.

Pharmacologically, 1-(4-nitrophenyl)-2-isopropylaminoethanol (INPEA) has been shown to be an effective adrenergic β-receptor antagonist.[2-8] Clinically, INPEA has been shown to be of potential value in the treatment of various disorders.[9-12] The value of INPEA lies in its lack of local anesthetic activity and freedom from intrinsic sympathomimetic activity.

To improve the pharmacological and clinical utility of INPEA, we have prepared the two optical isomers of INPEA[13] and established chemically their absolute configuration.

Resolution of INPEA was achieved by fractional crystallization of the salt of D-(−)-dibenzoyltartaric acid. The less soluble (+)-INPEA D-(−)-dibenzoyltartrate was easily purified by recrystallization from ethanol. From the mother liquors, (−)-INPEA D-(−)-dibenzoyltartrate was obtained.

To establish the absolute configuration at the asymmetric center, (−)-INPEA was converted into (−)-1-(4-hydroxyphenyl)-2-isopropylaminoethanol (V); this last compound was also prepared, starting from (D-(−)-1-(4-hydroxyphenyl)-2-aminoethanol (D-(−)-octopamine, VI), the absolute configuration of which is known.[14,15] Scheme I shows these reactions.

The absolute values of rotation of (−)-V obtained *via* the two routes were not equal, due to the facile racemization of the diazonium fluoroborate, (+)-IV, during its hydrolysis to (−)-V.

To establish that reductive condensation of the optical isomers of phenylethanolamines with ketones does not influence rotation, (−)-1-(4-methoxyphenyl)-2-aminoethanol, (−)-1-(3-hydroxyphenyl)-2-aminoethanol,[16] and (−)-1-(4-aminophenyl)-2-aminoethanol[17] were synthesized and reductively alkylated with acetone or 2-butanone. We obtained (−)-1-(4-methoxyphenyl)-2-isopropylaminoethanol, (−)-1-(3-hydroxy-

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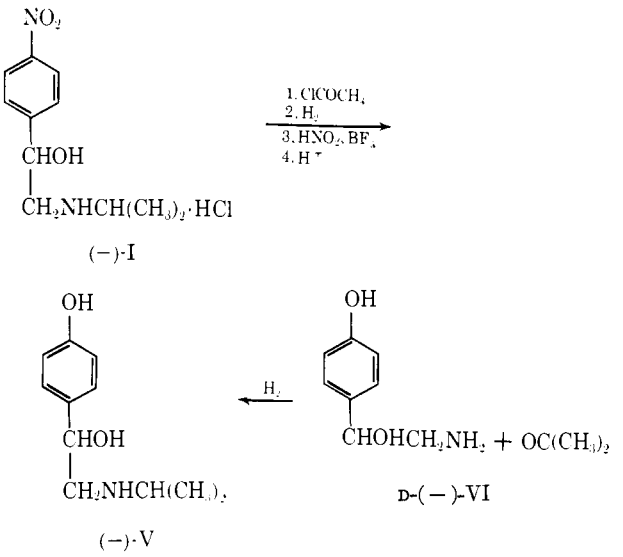
SCHEME I



phenyl)-2-isopropylaminoethanol, and (−)-1-(4-aminophenyl)-2-*sec*-butylaminoethanol,[17] respectively.

The N-acyl derivatives (II and IV) had rotations of opposite sign to that of the corresponding 2-aminophenylethanols.

Pharmacological Assay.—In this investigation, L-(+)-INPEA and D-(−)-INPEA were tested for their ability to antagonize the following adrenergic β-receptor responses in rats: the positive chronotropic response to epinephrine (EPI), the calorigenic action produced by epinephrine, and the arterial depressor response to isoproterenol (IS).

Pharmacological Methods.—Two types of experiments were performed. In the first, responses to slow intravenous infusions of epinephrine (producing cardioacceleration and increased respiratory metabolism) were obtained in control animals and in animals pretreated with L-(+)-INPEA or D-(−)-INPEA. The epinephrine was infused (10 μg/kg/min) *via* the right femoral vein using a polyethylene catheter and a Palmer constant infusion pump. The isomers were given at a dose of 50 mg/kg through a polyethylene tube introduced into the left femoral vein. Recordings of heart rate (by means of an electrocardiograph) and of oxygen consumption (by means of a CARLO ERBA metabolimeter for small animals) were made at 15-min intervals, once before and four times after dosing. The isomers were injected 30 sec before starting the epinephrine infusion.

In the second type of experiment the arterial depressor responses to 4 μg/kg of isoproterenol were obtained before and after administration of L-(+)-INPEA or D-(−)-INPEA. Blood pressure was measured from the right carotid artery with a mercury manometer and recorded on a kymograph. Fifteen minutes after a control response to 4 μg/kg of isoproterenol was obtained, L-(+)-INPEA or D-(−)-INPEA was given in the doses indicated in Figure 3 and the injection of isoproterenol was repeated, at 15-min intervals, four times. Time–depressor areas of the hypotensive phase produced by isoproterenol were measured with a planimeter in square millimeters and the values obtained were transformed to logarithms for statistical evaluation.

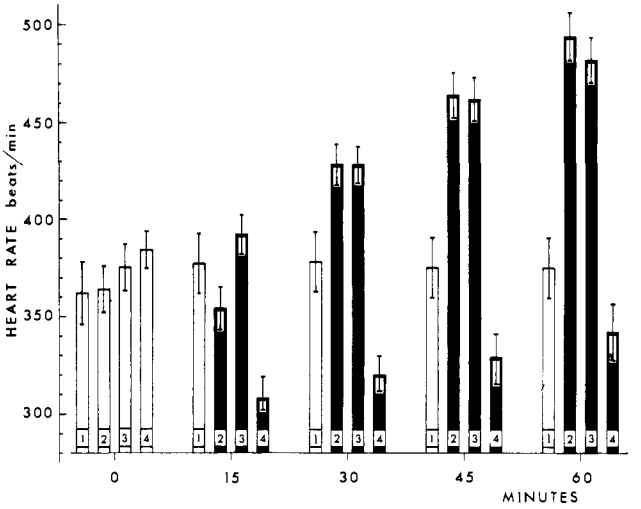


Figure 1.—Effect of L-(+)-INPEA and D-(−)-INPEA on the positive chronotropic action of epinephrine, administered by continuous intravenous infusion of 10 μg/kg/min in urethan-anesthetized, unatropinized rats. Both isomers were injected intravenously at the dose of 50 mg/kg at zero time and 30 sec prior to the beginning of epinephrine infusion. Bars represent mean values of heart rate in beats/min ± standard error, immediately before drug administration and 15, 30, 45, and 60 min after dosing. Treatment is indicated by the small numerals in the bars: (1) saline controls (n (number of animals) = 15), (2) epinephrine controls (n = 18), (3) L-(+)-INPEA (n = 15), (4) D-(−)-INPEA (n = 15).

The following drugs were used. Epinephrine hydrochloride (EPI), isoproterenol hydrochloride (IS), D-(−)-1-(4-nitrophenyl)-2-isopropylaminoethanol hydrochloride [D-(−)-INPEA], and L-(+)-1-(4-nitrophenyl)-2-isopropylaminoethanol hydrochloride [L-(+)-INPEA]. The doses of epinephrine and isoproterenol were calculated in terms of the base and those of the optical isomers of INPEA in terms of their salts.

Male Sprague–Dawley rats (not fasted) weighing between 185–205 g and anesthetized with 1.4 g/kg ip of ethylurethan were used throughout.

Effects of L-(+)-INPEA and D-(−)-INPEA on EPI-Induced Tachycardia (Figure 1).—Due to the vagal reflex bradycardia, there was a 15 to 20 min delay after starting the EPI infusion before the cardioaccelerator effect of the catecholamine became apparent in the control animals. Thereafter, the heart rate increased progressively throughout the EPI administration. L-(+)-INPEA in a standard dose of 50 mg/kg had no effect on the positive chronotropic response to EPI though it reduced the initial vagal slowing. The 50-mg/kg dose of D-(−)-INPEA, on the contrary, not only completely prevented the chronotropic effects of EPI but also markedly reduced the heart rate with respect to the control values observed either in the same animals before dosing or in the untreated controls.

Effects of L-(+)-INPEA and D-(−)-INPEA on the Calorigenic Action of EPI (Figure 2).—In control animals, stimulation of the respiratory metabolism began within the first few minutes of the EPI infusion and oxygen consumption progressively increased during the catecholamine administration. L-(+)-INPEA, in a standard dose of 50 mg/kg, had no effect on this calorigenic response to EPI. However, D-(−)-INPEA,

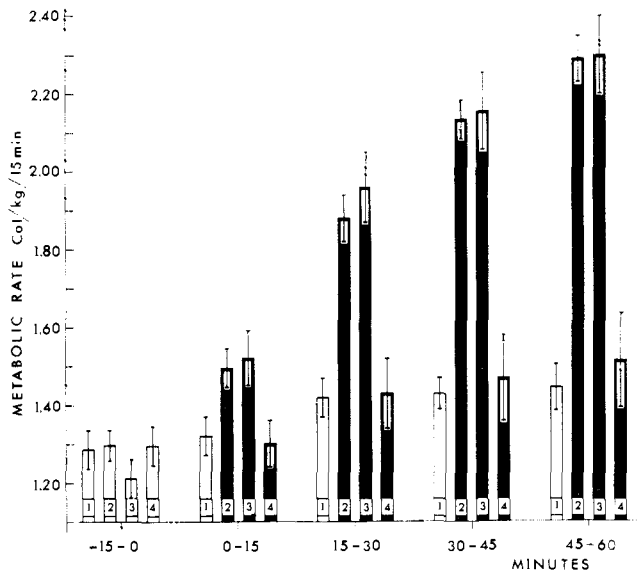


Figure 2.—Effect of L-(+)-INPEA and D-(−)-INPEA on the calorigenic action of epinephrine, administered by continuous intravenous infusion of 10 μg/kg/min in urethan-anesthetized, unatropinized rats. Both isomers were injected intravenously at the dose of 50 mg/kg at zero time and 30 sec prior to the beginning of epinephrine infusion. Bars represent mean values ± standard error of oxygen consumption in cal/kg/15 min, for each successive 15-min period beginning from 15 min before until 60 min after drug administration. Treatment is indicated by the small numerals in the bars: (1) saline controls (n (number of animals) = 15), (2) epinephrine controls (n = 18), (3) L-(+)-INPEA (n = 15), (4) D-(−)-INPEA (n = 15).

given at the same dose, completely prevented this EPI action for the duration of the experiment.

Effects of L-(+)-INPEA and D-(−)-INPEA on IS-Induced Arterial Depressor Response (Figure 3).—Acute intravenous injections of 4 μg/kg of IS produced marked hypotension. Whereas L-(+)-INPEA even given in very high doses (50 mg/kg) was found to be completely without effect on the IS-induced vasodilation, pretreatment with graded doses of D-(−)-INPEA resulted in a clear reduction of the hypotensive phase even after a single acute dose of only 1.56 mg/kg. This reduction of the IS depressor action was much more marked with the higher doses of D-(−)-INPEA, and antagonism was still present 60 min after dosing.

General Comments.—The results show clearly that the active adrenergic β-receptor blocking isomer of INPEA is (−)-1-(4-nitrophenyl)-2-isopropylaminoethanol hydrochloride (I) and that this compound has the D configuration. The D configuration has also been assigned to the active isomers of a series of catecholamines by La Manna and Ghislandi.[18] Although other β-receptor antagonists have been resolved into their optical isomers,[19-24] the absolute configuration at the asymmetric center to which the alcoholic hydroxyl is attached has not been chemically established.[25]

Resolution of adrenergic β-receptor antagonists into their optical isomers has already proved to be a useful method for distinguishing between their specific and nonspecific actions. Lucchesi[22] has shown that the dextrorotatory isomer of pronethalol which is not a β-receptor antagonist still has antiarrhythmic activity. This correlates with the evidence of Gill and Vaughan Williams[26] that pronethalol was not only twice as potent as quinidine as an antiarrhythmic agent but also as a local anesthetic. Thus the optical resolution of pronethalol has strengthened the evidence that the ability of pronethalol to antagonize cardiac glycoside induced arrhythmias is due to its local anesthetic action.

INPEA is interesting for its lack of local anesthetic[2,27,28] and nonspecific antiarrhythmic activity.[2,29] However, it still produces actions on the central nervous system (CNS). Recent work suggests that the actions of adrenergic β-receptor antagonists on the CNS, *i.e.*, the stimulant action of INPEA, and the depressant and anticonvulsant actions of propranolol and pronethalol, are also unrelated to β-receptor blockade.[30] Optical resolution of INPEA has been urgently needed to answer this question. Evidence that the D-(−) isomer of INPEA is the sole active form for β-receptor antagonism has recently been confirmed by Somani[31] and Fassina.[4] The availability of pure optical isomers of a β-receptor antagonist which is free from local anesthetic and CNS depressant actions should be invaluable for pharmacological analysis.

Experimental Section[32]

Resolution of 1-(4-Nitrophenyl)-2-isopropylaminoethanol.—1-(4-Nitrophenyl)-2-isopropylaminoethanol (100 g, 0.45 mole) was dissolved in 600 ml of boiling ethanol, and a solution of 172 g of D-(−)-dibenzoyltartaric acid monohydrate (0.46 mole) in 600 ml of boiling ethanol was added. After standing at room temperature for 3 days, the mixture was filtered and the solid was recrystallized from 900 ml of 85% ethanol. After chilling for 2 hr, the precipitate was filtered and recrystallized from 80% ethanol. The yield of (+) isomer was 105 g, after 12 hr at room temperature; mp 170–171°, $[\alpha]^{20}D$ −59.5° (c 2, ethanol).

All alcoholic mother liquors were concentrated to a small volume and the precipitate was filtered and recrystallized from dilute ethanol. (−)-1-(4-Nitrophenyl)-2-isopropylaminoethanol D-(−)-dibenzoyltartrate monohydrate (90 g) was obtained, mp 143–144°, $[\alpha]^{20}D$ −83.5° (c 2, ethanol).

(−)-1-(4-Nitrophenyl)-2-isopropylaminoethanol Hydrochloride (I).—(−)-1-(4-Nitrophenyl)-2-isopropylaminoethanol D-(−)-dibenzoyltartrate monohydrate (90 g) was suspended in water and the pH was adjusted to 11 with NaOH. The solid was filtered, washed with water until neutral, and taken up in warm 20% HCl. After decolorizing, the solution was cooled and the (−)-1-(4-nitrophenyl)-2-isopropylaminoethanol hydrochloride was filtered, mp 217–218°, $[\alpha]^{20}D$ −41° (c 2, water), $E^{1\%}_{1cm}$ 387 at 272 mμ.

Anal. Calcd for $C_{11}H_{17}ClN_2O_3$: C, 50.67; H, 6.57; N, 10.74; Cl, 13.60. Found: C, 50.59; H, 6.54; N, 10.79; Cl, 13.52.

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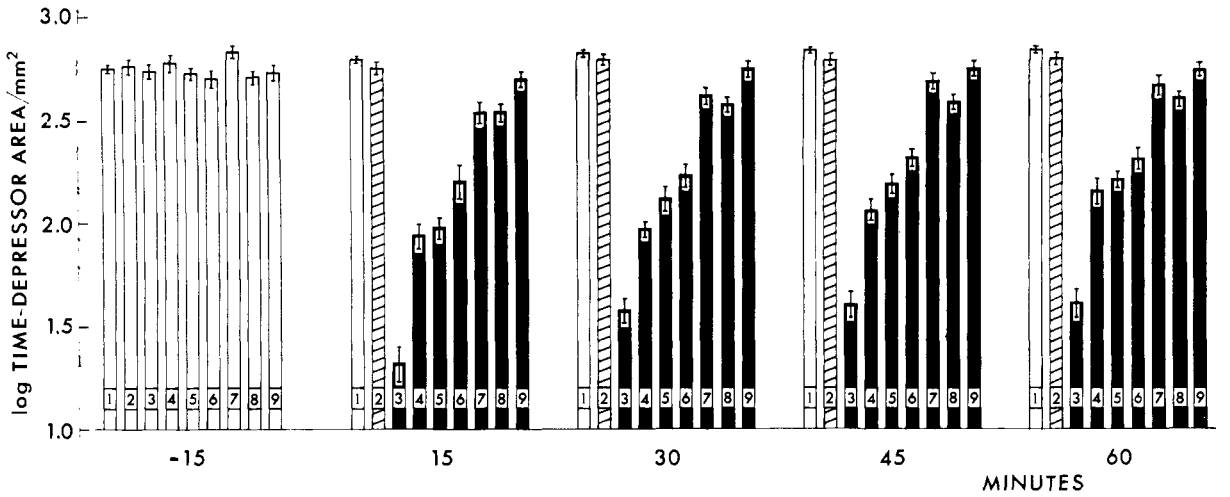

Figure 3.—Effect of intravenous L-(+)-INPEA and D-(−)-INPEA on the depressor response to 4 μg/kg of isoproterenol, injected intravenously in urethan-anesthetized, unatropinized rats. Bars represent mean values ± standard error of logarithms of the time-depressor areas, which is the area bounded on the one side by the mean pressure fall and on the other by a straight line drawn at the control pressure level from the start of the fall to the return to normotensive levels. Control panel (white bars) represents depressor responses to isoproterenol 15 min prior to administration of INPEA. Succeeding panels represent depressor responses at various intervals after administration of the isomer. Small numerals in the bars indicate (1) (white bars) controls (n (number of animals) = 74); (2) (hatched bars) L-(+)-INPEA, 50 mg/kg (n = 20); (3-9) (black bars) D-(−)-INPEA, 50 mg/kg (n = 23), 25 mg/kg (n = 10), 12.5 mg/kg (n = 11), 6.25 mg/kg (n = 10), 3.125 mg/kg (n = 10), 1.56 mg/kg (n = 10), and 0.78 mg/kg (n = 11).

(+)-1-(**4-Nitrophenyl**)-**2-isopropylacetamidoethanol** (II).—Acetyl chloride (13.2 g, 0.167 mole) and aqueous NaOH (13 g, 0.325 mole) were added slowly and simultaneously to a stirred aqueous solution of (−)-1-(4-nitrophenyl)-2-isopropylaminoethanol hydrochloride (40 g, 0.154 mole). The mixture was then stirred 15 min and extracted with chloroform. The solvent was washed with 5% HCl, dried, and evaporated *in vacuo*. The N-acetyl derivative (41 g) had mp 83–84°, $[\alpha]^{22}D$ +12.5° (*c* 2, ethanol).

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.55; H, 6.78; N, 10.43.

(+)-1-(**4-Diazophenyl**)-**2-isopropylacetamidoethanol Fluoroborate** (IV).—(+)-1-(4-Nitrophenyl)-2-isopropylacetamidoethanol (40 g, 0.150 mole), dissolved in 400 ml of ethanol, was hydrogenated in the presence of 4 g of palladium-on-charcoal catalyst, at room pressure. After the theoretical volume of hydrogen had been absorbed, the catalyst was filtered and the solvent removed *in vacuo*. The residue was dissolved in 300 ml of 1 *N* HCl, diazotized with 13 g of $NaNO_2$ (0.165 mole), and poured onto 13 g of H_3BO_3 dissolved in 35 ml of 50% HF. After the mixture had been concentrated, *in vacuo*, to 100 ml and chilled for 48 hr, it afforded the fluoroborate (50 g), mp 128–130°, $[\alpha]^{20}D$ +26° (*c* 2, water).

(−)-1-(**4-Hydroxyphenyl**)-**2-isopropylaminoethanol** (V). **A. From** (+)-1-(**4-Diazophenyl**)-**2-isopropylacetamidoethanol Fluoroborate** (IV).—The diazonium fluoroborate (+)-IV (48 g) was taken up in 220 ml of glacial acid and the mixture was gently warmed until the nitrogen was completely evolved. The solution was decolorized and concentrated *in vacuo* and the resulting residue was dissolved in water and washed with ether. The aqueous solution was acidified with 20% HCl, then gently warmed for 1 hr and finally refluxed for 15 min. After being cooled, the solution was neutralized with $NaHCO_3$ and the oil was extracted with ether. Concentration of the ether extract followed by distillation *in vacuo* afforded a colorless oil: bp 135–140° (0.3 mm); mp 79–81°; $[\alpha]^{20}D$ −10° (*c* 2, 1 *N* HCl); ultraviolet maxima at 220, 265, and 270 mμ.

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77; N, 7.17. Found: C, 67.51; H, 8.59; N, 7.08.

B. From D-(−)-1-(**4-Hydroxyphenyl**)-**2-aminoethanol** (VI).—D-(−)-1-(4-hydroxyphenyl)-2-aminoethanol[14] (2 g, 0.013 mole), $[\alpha]^{20}D$ −40° (*c* 1, 0.1 *N* HCl) (the product was about 70% optically pure), was dissolved in 20 ml of ethanol and 0.8 g of pure acetone (0.0138 mole) and 0.05 g of PtO_2 was added. The theoretical volume of hydrogen was absorbed in 3 hr. The ethanol was removed and the residue was crystallized from 2-propanol. D-(−)-1-(4-Hydroxyphenyl)-2-isopropylaminoethanol (1.5 g) was obtained, mp 80–81°, $[\alpha]^{20}D$ −31° (*c* 1, 0.1 N HCl). The melting point of this product was not depressed on admixture with the product obtained in A, and the two materials had identical ultraviolet spectra and chromatoplate values.

(−)-1-(**4-Methoxyphenyl**)-**2-aminoethanol**.—The resolution was accomplished with D-(−)-dibenzoyltartaric acid, substantially as described above for 1-(4-nitrophenyl)-2-isopropylaminoethanol. Two diastereoisomeric salts were obtained, respectively, with $[\alpha]^{20}D$ −62 and −90° (*c* 2, ethanol).

From this last, by basifying, extracting with ether, and bubbling HCl into the solution, (−)-1-(4-methoxyphenyl)-2-aminoethanol hydrochloride, mp 165–167°, $[\alpha]^{20}D$ −25° (*c* 2, water), was obtained. This product was probably 80% optically pure.

(−)-1-(**4-Methoxyphenyl**)-**2-isopropylaminoethanol**.—(−)-1-(4-Methoxyphenyl)-2-aminoethanol hydrochloride (10 g, 0.049 mole) was mixed in 40 ml of anhydrous ethanol with powdered NaOH (2 g, 0.05 mole). After being boiled for a few minutes, the mixture was cooled and filtered, and 3 g of pure acetone (0.051 mole) and 0.1 g of PtO_2 were added. Hydrogen was then admitted and after 3 hr, the theoretical quantity had been absorbed. The solvent was removed *in vacuo* and the residue crystallized from ethanol, mp 101–102°, $[\alpha]^{20}D$ −22.5° (*c* 2, 0.1 *N* HCl).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.79; H, 9.09; N, 6.58.

(−)-1-(**3-Hydroxyphenyl**)-**2-aminoethanol Hydrochloride**.—The resolution was accomplished, as described previously,[15] with D-(−)-dibenzoyltartaric acid by recrystallizing the two diastereoisomeric salts from dilute ethanol. These salts had, respectively, $[\alpha]^{20}D$ −78 and −104° (*c* 2, ethanol).

From this last, by basifying, extracting with ether, and bubbling HCl into the solution, (−)-1-(3-hydroxyphenyl)-2-aminoethanol hydrochloride, mp 163–164°, $[\alpha]^{20}D$ −25° (*c* 2, water), was obtained.

(−)-1-(**3-Hydroxyphenyl**)-**2-isopropylaminoethanol**.—The product was obtained as described above for the 4-methoxy derivative, mp 132–133° and $[\alpha]^{20}D$ −22° (*c* 2, 0.1 *N* HCl).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77; N, 7.17. Found: C, 67.59; H, 8.68; N, 7.13.