TABLE I: SUBSTITUTED ETHYLENEDIAMINES IV

No.	N(R1)(R2)	Bp (mm) or mp of base, °C	Mp of hydrochloride, °C	Crystn solvent	Formula[b]	Pressure response, mm: Dose, mg/kg	Fall	Rise
1	*N*-Piperidino	193–195 (4–6)	278–279	A[c]	$C_{14}H_{27}N_3O_2 \cdot 2HCl$	25	Nil	Nil
2	*N*-Morpholino	220–222 (10–12)	285–286	A	$C_{13}H_{25}N_3O_3 \cdot 2HCl$	25	Nil	Nil
3	*N*-Pyrrolidino	173–175 (4–6)	295–296	B	$C_{13}H_{25}N_3O_2 \cdot 2HCl$			
4	*N*-1,2,3,4-Tetrahydroisoquinolino	248–250 (8–10)	265–267	A	$C_{18}H_{27}N_3O_2 \cdot 2HCl$	10	62	Nil
5	4-Benzyl-1-piperazino	253–255 (4–6)	261–262	A	$C_{20}H_{32}N_4O_2 \cdot 2HCl$	25	41	Nil
6	4-*p*-Chlorophenyl-1-piperazino	97	264–265	B	$C_{19}H_{29}ClN_4O_2 \cdot 2HCl$	25	Biphasic	
7	4-Phenylpiperazino	*a*	264–266	A	$C_{19}H_{30}N_4O_2 \cdot 2HCl$	25	Nil	Nil
8	4-*m*-Chlorophenyl-1-piperazino	263–265 (4–6)	266–268	A	$C_{19}H_{29}ClN_4O_2 \cdot 2HCl$	10	55	Nil
9	*i*-Pr_2N	184–187 (4–6)	232–235	C	$C_{15}H_{31}N_3O_2 \cdot 2HCl$	25	Nil	Nil

[a] Decompd during distn. [b] All HCl salts were analyzed for C, H, N, Cl, and the anal. results were within ±0.4% of the theoretical values. [c] A, MeOH; B, EtOH; C, EtOH–Et_2O.

dures.[18] In these, 1,4-piperazinedicarboxylic acid Et ester is invariably formed along with 1-piperazinecarboxylic acid Et ester. Further the methods are tedious and work-up is difficult. In the present procedure, formation of the disubstituted product has been totally avoided. 1-Piperazinecarboxaldehyde[19] is first converted to 4-formyl-1-piperazinecarboxylic acid Et ester[20] which on hydrolysis with NaOH (10%) for 4 hr gave 1-piperazinecarboxylic acid Et ester in 85–90% yield.

Substituted Ethylenediamines IV.—A mixt of 4-(β-chloroethyl)-1-piperazinecarboxylic acid Et ester·HCl (0.05 mole), the appropriate secondary amine (0.05 mole), anhyd K_2CO_3 (0.05 mole), and abs EtOH (50 ml) was refluxed for about 6 hr, and the solvent was removed by distn. The residual material was treated with H_2O and the aq soln after basification with 50% NaOH soln to pH 9 was extd with Et_2O The ext was dried (Na_2SO_4) and concd to afford the desired product as liq which was distd *in vacuo*. In all cases the viscous liquids finally obtd were converted into the corresponding hydrochlorides by passing dry HCl through an Et_2O soln. All compds were characterized as their hydrochlorides. Only **6** (see Table I) gave an anal. pure sample of the base on crystn from petr ether (bp 60–80°). The characteristics of IV have been recorded in Table I.

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(18) (a) T. S. Moore, M. Boyle, V. M. Thorn, *J. Chem. Soc.*, **39**, (1929); (b) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2570 (1956); (c) K. R. Jacobi, *Ber.*, **B66**, 113 (1933).

(19) K. Fujii, K. Tomino, and H. Watanabe, *Yakagaku Zasshi*, **74**, 1049 (1954).

(20) (a) W. Logemann, D. Artini, and G. Tosolini, *Chem. Ber.*, **91**, 2566 (1958); (b) conversion of 1-piperazinecarboxaldehyde to 4-formyl-1-piperazinecarboxalic acid Et ester is more advantageous than to convert 1-piperazinecarboxalic acid Et ester to 4-formyl-1-piperazinecarboxalic acid Et ester according to the method of Logemann, *et al.*[20a]

Optical Isomers of Mepivacaine and Bupivacaine

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Current interest in the potent local anesthetics mepivacaine and bupivacaine—*N*-methyl and *N*-butyl derivatives of (±)-2′,6′-pipecoloxylidide—(I) prompted us to prepare and study the optical isomers. The parent (±)-I was resolved using dibenzoyl (+)-tartaric acid. Mepivacaine was resolved by crystallization of its quinic acid salts.[1] Although a number of optically active acids were tried as resolving agents for (±)-bupivacaine, no separation of the isomers could be effected until seed crystals were made available by N-butylation of (−)-I and crystallization of its salt with (+)-tartaric acid.

An observation that (+)-mepivacaine·HCl and (−)-bupivacaine·HCl were significantly longer acting than their enantiomers has been reported in an earlier publication from this laboratory.[2] Thus it became of interest to establish their configuration. This was accomplished by preparing from (*R*)-(+)-methyl pipecolate[3] and 2,6-xylidinomagnesium bromide[4] the parent (*R*)-(−)-I identical with (−)-I by resolution of (±)-I. N-Butylation of a sample of this (*R*)-I gave (*R*)-(+)-bupivacaine and N-methylation of (*S*)-I (obtained from resolution of (±)-I) gave (*S*)-(+)-mepivacaine. Thus, the longer-acting (+)-mepivacaine and (−)-bupivacaine isomers are both of the (*S*) configuration.

Experimental Section

Resolution of 2′,6′-Pipecoloxylidide (I).—To a soln of 42.0 g (0.15 mole) of (±)-I in 300 ml of boiling *i*-PrOH was added a soln of 38.0 g (0.10 mole) of dibenzoyl (+)-tartaric acid monohydrate (DBT) in 300 ml of boiling *i*-PrOH. Immediate crystn occurred which was completed by slow stirring while the mixt cooled to 35°. The ppt was collected, washed with *i*-PrOH, and dried at 70° to give 32 g of (+)-base DBT salt, mp 186–189°. This crop was converted to base by suspending in 300 ml each of H_2O and Et_2O and adding 8 ml of 28% NH_4OH. The Et_2O layer was sepd, washed with H_2O, and concd *in vacuo*. The residue was crystd from boiling hexane to give a 12.0-g first crop of the base, mp 130–132°, $[\alpha]^{25}D$ +46.1° (*c* 2.3, 1 *N* HCl). This rotation was unchanged after recrystn from *i*-PrOAc.

The resoln liquor was evapd *in vacuo*, and the residual crude (−)-base DBT salt was converted to base as above and recrystd twice from boiling hexane to give 11.1 g of base, mp 130–132°, $[\alpha]^{25}D$ −46.8° (*c* 2.3, 1 *N* HCl), $[\alpha]^{25}D$ −11.04 (*c* 5, MeOH).

Resolution of (±)-Mepivacaine.—A soln of 46.0 g (0.186 mole) of (±)-mepivacaine (mp 149–151°) with 38.4 g (0.2 mole) of quinic acid (Freas Bros.) and 400 ml of abs EtOH was seeded at 60° and stirred and cooled to 25°. The cryst ppt was collected and recrystd from 300 ml of 95% EtOH to give 34 g of (+)-base quinate, mp 192–195°. This salt was dissolved in 300 ml of H_2O and basified slowly with NH_4OH while rubbing and stirring to induce crystn. The pptd base was collected, washed with H_2O,

(1) B. T. Ekenstam, B. von Egner, and G. Petterson, *Acta Chem. Scand.*, **11**, 1183 (1957), who resolved mepivacaine "with the aid of tartaric acid" but gave no details.

(2) F. P. Luduena, *Annu. Rev. Pharmacol.*, **9**, 503 (1969).

(3) P. S. Portoghese, T. L. Pazdernik, W. L. Kuhn, G. Hite, and A. Shafi'ee, *J. Med. Chem.*, **11**, 12 (1968).

(4) Thuresson and Egner, U. S. Patent 2,799,679. These authors used the Bodraux reaction to prepare several racemic 2,6-xylidides.

and dried at 70° to give 19.0 g of nearly pure base. A 1-g portion recrystd from *i*-PrOAc melted at 153–155°, $[\alpha]^{25}D$ −63° (*c* 5, MeOH). A 10-g sample of the base was dissolved in 100 ml of *i*-PrOH and neutralized by addn of 3.9 ml of concd HCl. The mixt was cooled to 5° and filtered to give, after drying, 8.0 g of (+)-base·HCl, mp 293–295°, $[\alpha]^{25}D$ +19° (*c* 0.5, H_2O). *Anal.* ($C_{15}H_{23}ClN_2O$) Cl.

Evapn of the resoln liquor and conversion of the residue to the base as above yielded 25 g of the crude enantiomer. This material was treated with 17 g of (+)-tartaric acid in 400 ml of 95% EtOH, and the soln was kept several hr at 25°. A total of 30 g of salt, mp 83–85°, was isolated, and recrystn from 30 ml of H_2O at 5° gave 25 g of pure (+)-bitartrate, mp 100–101°. This salt was converted to base as above (12.7 g) which by neutralization with concd HCl in *i*-PrOH gave 12.0 g of (−)-base·HCl, mp 293–295°, $[\alpha]^{25}D$ −18.6° (*c* 5, H_2O). *Anal.* ($C_{15}H_{23}ClN_2O$) Cl. A sample of the base prepd from this salt melted at 153–155°, $[\alpha]^{25}D$ +63° (*c* 5, MeOH).

Resolution of (±)-Bupivacaine.—A soln of 412 g (1.42 moles) of (±)-bupivacaine base and 216 g (1.44 moles) of (+)-tartaric acid in 1500 ml of boiling *i*-PrOH was seeded and kept at 5° for 2 hr with occasional swirling. The heavy ppt was filtered, washed with *i*-PrOH, and dried to yield 200 g of nearly pure (+)-base (+)-tartrate, mp 183–184°, unchanged by recrystn from *i*-PrOH. A 10.2-g portion of this salt was converted to base (dil NH_4OH, H_2O, and Et_2O) to give 7.6 g or crude (+)-base, mp 128°. Recrystn from 30 ml of *i*-PrAcO gave 6.5 g pure (+)-base, mp 135–137°, $[\alpha]^{25}D$ +81° (*c* 5, MeOH).

This base was dissolved in 50 ml of hot *i*-PrOH and neutralized by the addn of 2.3 ml of concd HCl. After evapn *in vacuo* the residue was crystd from 30 ml of *i*-PrOH to give 6.0 g of (+)-base·HCl, mp 258°, $[\alpha]^{25}D$ +12.7° (*c* 2, H_2O). *Anal.* ($C_{18}H_{24}ClN_2O$) Cl, N.

The resoln liquor on standing at 25° with occasional scratching and swirling gave after 5 hr 400 g of crude (−)-bupivacaine (+)-tartrate, mp 110–115°. This fraction was dissolved in 2 l. of H_2O and slowly basified with 28% NH_4OH, to ppt 250 g of (−)-rich base. Recrystn from 500 ml of *i*-PrOH gave 120 g, mp 132–134°, which was recrystd from 500 ml of *i*-PrOH to yield 109 g of pure (−)-base, mp 135–137°, $[\alpha]D^{25}$ −80.9° (*c* 5, MeOH). Conversion to the HCl salt as described above for (+)-base gave 110 g of (−)-base·HCl, mp 255–257°, $[\alpha]^{25}D$ −12.3° (*c* 2, H_2O). *Anal.* ($C_{18}H_{31}ClN_2O$) Cl, N.

(*R*)-(−)-2′,6′-Pipecoloxylidide.—To an EtMgBr soln, prepd from 1.4 g of Mg and 6.6 g of EtBr in 100 ml of dry Et_2O, was added dropwise 4.8 g of 2,6-xylidine with stirring during strong gas evoln. (*R*)-(+)-Methyl pipecolate (1.8 g) was added rapidly, and stirring was contd at room temp for 15 min followed by a 30-min reflux period. The mixt was cooled to 25° and 100 ml of 1 *N* HCl was added slowly. The pH was adjusted to 5.5 by the addn of 10% NaOH soln. The Et_2O layer was sepd, and the aq layer was reextd with 100 ml of Et_2O. The combined Et_2O extracts contained the unreacted xylidine.

The aq portion was basified with excess NH_4OH, and the resulting $Mg(OH)_2$ slurry was extd twice with 100 ml of *i*-PrAcO. Evapn of the solvent *in vacuo* left a crystn residue which was recrystd from boiling hexane to give 0.7 g of (*R*)-(−)-**I**, mp 130°; mmp with (−)-I obtained by resoln was not depressed, and $[\alpha]^{25}D$ −46° (*c* 2.3, 1 *N* HCl) was in agreement with that of the latter.

(*S*)-(−)-Mepivacaine by N-Methylation of (*S*)-(+)-I.—A soln of 4.6 g of (*S*)-(+)-I with 4 ml of 40% formalin in 200 ml of abs EtOH was hydrogenated over 2 g of 10% Pd/C at 25° and 2.82 kg/cm² of H_2 to a 1-equiv H_2 uptake in 3 hr. After removal of catalyst and vacuum evapn of solvent, a cryst residue remained, which after recrystn from boiling hexane gave 2.15 g of (*S*)-(−)-mepivacaine, mp 148–152° and $[\alpha]^{25}D$ −62.3° (*c* 5, MeOH). This base (0.184 g) dissolved with 0.154 g of quinic acid in 2 ml of abs EtOH at boiling gave rapid crystn of the (+)-base quinate (0.31 g), mp 194–197°; mmp with the (+)-base quinate obtd by resoln was not depressed.

(*R*)-(+)-Bupivacaine by N-Butylation of (*R*)-(−)-I.—A soln of 2.32 g of (*R*)-(−)-I and 2.0 g of *n*-BuBr in 25 ml of BuOH with 1.15 g of anhyd K_2CO_3 was stirred and heated under gentle reflux for 18 hr. After filtration from inorganic salts, the BuOH was dist off *in vacuo*. The residue with 0.75 g (+)-tartaric acid gave 2.8 g of (*R*)-(+)-bupivacaine-(+)-tartrate from 10 ml of boiling *i*-PrOH, mp 182–184°, characteristic of the (+)-enantiomer which on conversion *via* base to the HCl salt gave 1.8 g of (*R*)-(+)-base·HCl, mp 253–255°, $[\alpha]^{25}D$ +12.5° (*c* 2, H_2O); mmp with HCl salt obtd by direct resoln was not depressed.

2-Aminoindan-2-carboxylic Acids. Potential Tyrosine Hydroxylase Inhibitors

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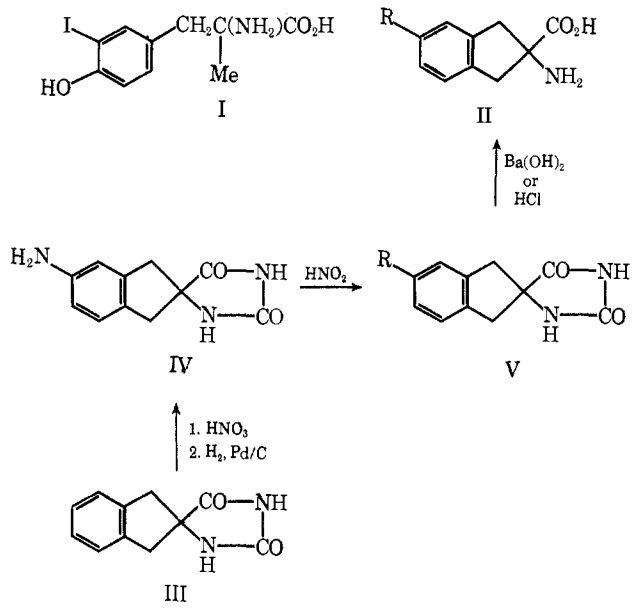
Tyrosine hydroxylase is an important enzyme for control of catecholamine levels *in vivo*, since its catalysis of the conversion of L-tyrosine to L-dopa is the rate-determining step in catecholamine biosynthesis.[1] The most potent inhibitors of this enzyme are the α-Me aromatic amino acids,[2-4] particularly close structural relatives of the natural substrate, such as 3-iodo-α-methyltyrosine (I). We have synthesized a series of 2-aminoindan-2-carboxylic acids (II), in which the α-Me group is incorporated into the indan ring, in an attempt to define the active site of tyrosine hydroxylase.

Nitration[5] of the spirohydantoin III derived from indan-2-one, followed by catalytic reduction, gave the key intermediate, spiro(5-aminoindan)-2,5′-hydantoin (IV). Diazotization allowed introduction of a variety of 5 substituents, and the resulting hydantoins V were decomposed to the desired amino acids by the use of either concd HCl in a sealed tube at 160° or refluxing aq $Ba(OH)_2$.[3]



In behavioral tests in rats, none of the compds in Table I affected spontaneous motor activity[6] or conditioned avoidance responses,[7] suggesting an absence of

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