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.* ($C_{15}H_{24}ClN_2O$) 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.* ($C_{15}H_{24}ClN_2O$) 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* 2.5, 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 crysl 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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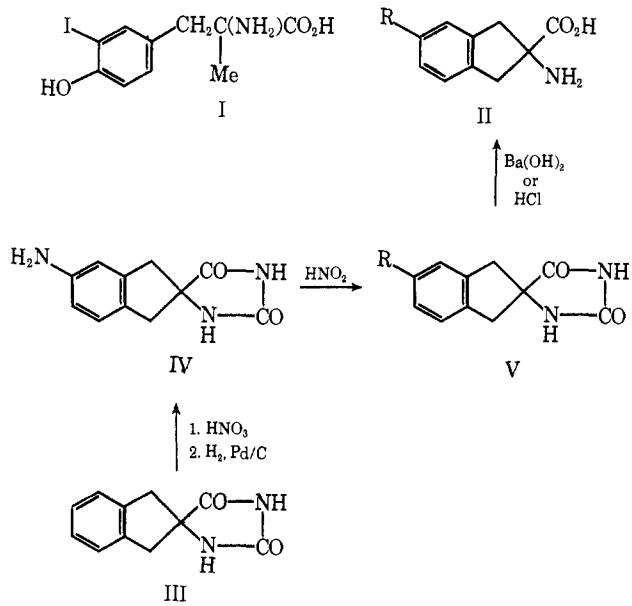
Tyrosine hydroxylase is an important enzyme for control of catecholamine levels *in vivo*, since its catalysis of the conversion of L-tyrosine to L-dopa is the rate-determining step in catecholamine biosynthesis.[1] The most potent inhibitors of this enzyme are the α-Me aromatic amino acids,[2–4] particularly 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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(3) W. S. Saari, J. Williams, S. F. Britcher, D. E. Wolf, and F. A. Kuehl, *J. Med. Chem.*, **10**, 1008 (1967); R. E. Counsell, P. Desai, T. D. Smith, P. S. Chan, P. A. Weinhold, V. B. Rethy, and D. Burke, *ibid.*, **13**, 1040 (1970).

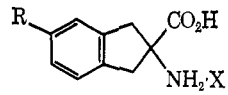
(4) S. Udenfriend, P. Zaltzman-Nirenberg, and T. Nagatsu, *Biochem. Pharmacol.*, **14**, 837 (1965); E. G. McGeer and P. L. McGeer, *Can. J. Biochem.*, **45**, 115 (1967); B. N. Lutsky and N. Zenker, *J. Med. Chem.*, **11**, 1241 (1968).

(5) A. B. Mauger and W. C. J. Ross, *Biochem. Pharmacol.*, **11**, 847 (1962).

(6) P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).

(7) R. W. Brimblecombe, in "Modern Trends in Toxicology," E. Boyland and R. Goulding, Ed., Butterworths, London, 1968, pp 149–174.

TABLE I



R	X	Method	Yield, %	Mp, °C[a]	Formula[b]	Hall's open field test,[c] minimum effective dose, mg/kg, sc, and time to effects[d]	Effects[e]
H	HCl	A	42	260–262[f]	$C_{10}H_{11}NO_2 \cdot HCl$	>10	
OH		B	34	252–254	$C_{10}H_{11}NO_3$[g]	5 (1.5 hr)	↓ D, ↓ F
OMe		B	65	269–271	$C_{11}H_{13}NO_3$[h]	>10	
CO_2H	HCl	A	21	296–300	$C_{11}H_{11}NO_4 \cdot HCl$		
Cl	HCl	A	72	249–251	$C_{10}H_{10}ClNO_2 \cdot HCl$	1 (1.5 hr)	↓ P, ↑ SQ
Br	HCl	A	40	275–278	$C_{10}H_{10}BrNO_2 \cdot HCl$	5 (3 hr)	↓ R, ↑ CS
I	HCl	A	18	240–243	$C_{10}H_{10}INO_2 \cdot HCl$	>10	

[a] All compds were recrystd from H_2O. [b] All compds were anal. for C, H, N. [c] R. W. Brimblecombe, *Psychopharmacologia*, **4**, 139 (1963). [d] All compds had LD_{50} values greater than 50 mg/kg, iv. [e] ↑ increase, ↓ decrease, D = times defecating, F = number of fecal boluses, P = times preening, SQ = number of squares crossed, R = times rearing, CS = number of central squares crossed. [f] Although reported by P. E. Gagnon and J. L. Boivin, *Can. J. Res., Sect. B*, **26**, 503 (1948), no details are given. [g] Found: N, 7.74. $C_{10}H_{11}NO_3$ requires N, 7.25%. [h] Found: N, 7.36. $C_{11}H_{13}NO_3$ requires N, 6.76%.

central stimulant or excitatory properties. However, in Hall's open field test,[8] the 5-Cl, 5-OH, and 5-Br derivatives showed activity at low doses similar to that observed with animals treated with psychotomimetics such as LSD under the same test conditions. Nevertheless, it is doubtful whether these effects are related to any action on catecholamine biosynthesis because the chief behavioral sign of known tyrosine hydroxylase inhibitors is sedation, and this is apparent only at high doses.[9] Certainly, after 15-min preincubation with the enzyme *in vitro*,[2] the compds ($10^{-3}M$) produced inhibition of less than 10%, conditions under which 3-iodotyrosine produced 95% inhibition. It is probable that the rigidity and symmetry incorporated into the structure compared with the α-Me aromatic amino acids may well be responsible for this relative lack of activity; a similar conclusion has been reached regarding 2-amino-5,6-dihydroxyindan-2-carboxylic acid, the analog of α-Me-dopa.[10] Dreiding models show that the conformation of the 2-aminoindan-2-carboxylic acids differs markedly from the active conformations recently proposed for L-tyrosine and L-dopa, the respective substrates for tyrosine hydroxylase and dopa decarboxylase.[11]

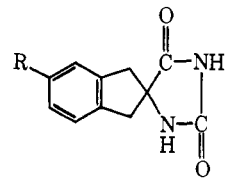
Experimental Section[12]

Spiro(5-nitroindan)-2,5′-hydantoin.—A soln of spiro(indan)-2,5′-hydantoin[5] (36 g) in HNO_3 (*d* 1.4, 400 ml) was stirred at 30° for 1 hr, and was then poured onto crushed ice (1 kg). The pale yellow cryst solid was filtered, washed with H_2O, dried, and recrystd from EtOH as yellow needles, mp 255–258°, yield 30 g (68%). *Anal.* ($C_{11}H_9N_3O_4$) C, H, N.

Spiro(5-aminoindan)-2,5′-hydantoin (IV).—A soln of 30 g of spiro(5-nitroindan)-2,5′-hydantoin in EtOH (500 ml) was shaken in a Parr hydrogenator under 2.8 kg/cm² of H_2 in the presence of 3 g of 10% Pd/C. When no more H_2 was absorbed (*ca.* 2 hr), the catalyst was removed by filtration and washed well with hot EtOH (1 l.), and the combined filtrate and washings were evapd to the point of crystn. The product was obtd pure as colorless plates, mp 221–223°, yield 24.5 g (92%). *Anal.* ($C_{11}H_{11}N_3O_2$) C, H, N.

Spiro[5-(substituted)indan]-2,5′-hydantoins (V).—In a typical example, IV (2.2 g, 10 mmoles) was dissolved in 10% H_2SO_4 (40 ml), the soln was cooled to 0°, and $NaNO_2$ (0.7 g, 10 mmoles) in H_2O (10 ml) was added so that the temp remained below 5°. After stirring for 1 hr at 0–5° the clear brown diazonium soln was decompd by heating to 70° until the evoln of N_2 ceased. Physical constants are recorded in Table II; substituents other than OH were introduced by decompn of the diazonium salt in boiling MeOH (OMe), KI soln at 60° (I), HBr and CuBr at 70° (Br), HCl and CuCl at 70° (Cl), and CuCN and NaCN at 70° (CN).

TABLE II



R	Yield, %	Mp, °C	Recrystn solvent	Formula[a]
H	66	262–264[b]	EtOH	$C_{11}H_{10}N_2O_2$
NO_2	68	255–258	EtOH	$C_{11}H_9N_3O_4$
NH_2	92	221–223	EtOH	$C_{11}H_{11}N_3O_2$
OH	70	300–303	H_2O	$C_{11}H_{10}N_2O_3$
OMe	64,[c] 52[d]	216–217	EtOAc	$C_{12}H_{12}N_2O_3$
CN	26	258–260	EtOH	$C_{12}H_9N_3O_2$
Cl	58	246–248	AcOH–H_2O	$C_{11}H_9ClN_2O_2$
Br	62	280–282	AcOH–H_2O	$C_{11}H_9BrN_2O_2$
I	48	273–276	AcOH–H_2O	$C_{11}H_9IN_2O_2$[e]

[a] All compds were anal. for C, H, N. [b] Lit.[5] 260–267°. [c] By methylation of the OH compd with Me_2SO_4–NaOH. [d] By decompn of the diazonium salt in MeOH; a small amt (<10%) of the OH compd was removed by chromatog. [e] Found: N, 9.09. $C_{11}H_9IN_2O_2$ requires N, 8.54%.

2-Amino-5-(substituted)indan-2-carboxylic acids (II). Method A.—Typically, spiroindan-2,5′-hydantoin (6 g) and concd HCl (60 ml) were heated at 160° for 2 hr in a sealed tube. The resulting soln was decolorized with charcoal, filtered, and concd to crystn. Recrystn was performed by dissoln in boiling H_2O and concn to the point of crystn.

Method B.—For example, a mixt of spiro(5-hydroxyindan)-2,5′-hydantoin (4.4 g, 20 mmoles), $Ba(OH)_2 \cdot 8H_2O$ (12 g), and H_2O (50 ml), was stirred and refluxed under N_2 for 64 hr. H_2O (100 ml) was added to the cooled mixt which was satd with CO_2, filtered, decolorized, and concd to crystn.

(8) R. W. Brimblecombe, *Psychopharmacologia*, **4**, 139 (1963).

(9) S. Spector, A. Sjoerdsma, and S. Udenfriend, *J. Pharmacol. Exp. Ther.*, **147**, 86 (1965); G. A. Johnson, E. G. Kim, W. Veldkamp, and R. Russell, *Biochem. Pharmacol.*, **16**, 401 (1967); M. L. Torchiana, C. C. Porter, C. A. Stone, and H. M. Hanson, *ibid.*, **19**, 1601 (1970).

(10) J. B. Taylor, J. W. Lewis, and M. Jacklin, *J. Med. Chem.*, **13**, 1226 (1970).

(11) J. W. Becker, Y. T. Thathachari, and P. G. Simpson, *Biochem. Biophys. Res. Commun.*, **41**, 444 (1970).

(12) Melting points (uncor) were detd on an Electrothermal capillary app. Satisfactory ir, uv, and nmr spectra were recorded for all new compds. Where anal. are indicated only by elemental symbols, figures obtained were within ±0.4% of theor values.