Isopropylamino-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanol (20).—A mixture of 2-isopropylamino-1-(2-naphthyl)ethanol[18] (10 g, 0.0435 mole), EtOH (10 ml), and Raney Ni (1 g) was hydrogenated at 125° and 125 atm for 6 hr. The mixture was cooled, EtOH (50 ml) was added, the mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. HCl (2 *N*, 50 ml) was added to the residue and the solution was washed with Et_2O (50 ml). NaOH (11 *N*, 20 ml) was added to the aqueous acidic solution and the product which separated was isolated by Et_2O extraction. The extract furnished **20**, mp and mmp 84–85° from petroleum ether.

2-Isopropylamino-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanol (20) from 2-Benzylisopropylamino-1-(2-naphthyl)ethanol.—A solution of 2-benzylisopropylamino-1-(2-naphthyl)ethanol[18] (1 g, 0.003 mole) in EtOH (10 ml) containing concentrated HCl (0.05 ml) was hydrogenated in the presence of Pt (0.3 g). The mixture was filtered and the filtrate was evaporated to dryness. The residual solid (**20**) had mp and mmp 156–157° from EtOAc.

2-Isopropylamino-1-acenaphthenol (71).—Acenaphthenequinone monoxime[21] (2 g, 0.01 mole) was hydrogenated in EtOH (15 ml) and Me_2CO (20 ml, 0.27 mole) in the presence of Pt (0.43 g). The deep red mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc, decolorized by treatment with C, and then converted to the hydrogen oxalate, mp 184–186° dec from MeOH–Et_2O. *Anal.* ($C_{17}H_{19}NO_5$) C, H, N.

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The Synthesis of 2,4,5-Trihydroxyphenylalanine (6-Hydroxydopa). A Centrally Active Norepinephrine-Depleting Agent

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The synthesis of 2,4,5-trihydroxyphenylalanine (6-hydroxydopa) (III) was accomplished through the reaction of 2,4,5-tribenzyloxybenzyl bromide (II) with dibenzyl carbobenzyloxyaminomalonate, followed by reductive removal of the blocking groups and thermal decarboxylation of the resulting amino(2,4,5-trihydroxybenzyl)-malonic acid (VI). Alternate synthetic approaches (Schemes I and II) were unsuccessful. 6-Hydroxydopa was found to undergo enzymatic decarboxylation *in vitro* and *in vivo* to form 6-hydroxydopamine, a known norepinephrine-depleting agent. 6-Hydroxydopa in this way causes depletion of norepinephrine both in the peripheral and central nervous system. A concomitant reserpine-like syndrome is observed in mice.

Almost 10 years after the discovery of 2,4,5-trihydroxyphenethylamine (6-hydroxydopamine) as an autoxidation product and metabolite of dopamine[2–4] the importance of this amine as a pharmacological tool for the selective destruction of adrenergic nerve terminals has been realized.[5–7] The first metabolic studies with 6-hydroxydopamine indicated only the formation of O-methylated products *in vivo* and *in vitro*[8] while pharmacological studies indicated that its actions resembled that of guanethidine and reserpine.[9] These pharmacological effects were subsequently found to result from a prolonged depletion of peripheral norepinephrine and it was posulated that 6-hydroxydopamine produced an irreversible destruction of norepinephrine binding sites.[10] It was reported that free 6-hydroxydopamine or basic metabolites could not be detected in the heart 3 hr after administration of the drug,[11] but that when 6-hydroxydopamine-2′-^{14}C was utilized, radioactivity was found to persist in the heart for 2–3 weeks and to correlate with the extent of norepinephrine depletion.[12] It is now apparent that this persistent radioactivity results from an irreversible combination of 6-hydroxydopamine with tissue constituents.[7] The amine is actively concentrated by the adrenergic nerve terminal, where at low concentrations it serves as a "false transmitter," while at high concentrations it first functionally impairs nerve transmission and then produces degeneration of the nerve terminal.[7] These results are in agreement with the observations that depletion of norepinephrine by 6-hydroxydopamine is prevented[13–15] by agents such as cocaine, metaraminol, and desmethylimipramine which are known to inhibit the active transport of amines at the axon membrane.[16] Reserpine, however, does not appear to prevent depletion of norepinephrine by 6-hydroxydopamine.[14,15] This suggests that uptake of 6-hydroxydopamine by the norepinephrine storage granule, which presumably should be blocked by reserpine,[16] is not necessary to the activity of this drug. Bretylium, on the other hand, blocks the release of norepinephrine by reserpine and that caused by 6-hydroxydopamine as well.[14,15]

Related amines such as 6-hydroxynorepinephrine and 6-hydroxyepinephrine were also found to cause release of cardiac norepinephrine-^3H,[17] but neither of these compounds was as stable or as effective in causing depletion of norepinephrine as 6-hydroxydopamine. Two other compounds, α-methyl-6-hydroxydopamine and 6-aminodopamine, have been reported[13] as similar in action to 6-hydroxydopamine. No depletion of brain norepinephrine has been observed[13,14] with these amines,

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as catecholamines, in contradistinction to their amino acid precursors, do not readily pass the blood–brain barrier. Thus, 6-hydroxydopamine, an agent which can produce a peripheral "chemical sympathectomy," is a most promising instrument for studies on the function of the sympathetic nervous system.

In the present study, we report the synthesis of 2,4,5-trihydroxyphenylalanine (6-hydroxydopa), its enzymatic decarboxylation to 6-hydroxydopamine both *in vitro* and *in vivo*, and both the peripheral and central depletion of norepinephrine following administration of this amino acid.

Experimental Section

All melting points are corrected unless otherwise noted; ir spectra were recorded in chloroform solutions with a Perkin-Elmer spectrophotometer Model 421; nmr spectra were obtained on a Varian A-60 spectrometer using TMS as internal standard. Silica gel GF 253 plates (Brinkman Instruments) were used for both analytical and preparative tlc.

1,2,4-Tribenzyloxybenzene was prepared as described previously.[18] The yield could be increased to 75% if the reaction mixture was allowed to reflux for 72 hr under N_2. Purification of the crude, oily product was carried out by column chromatography on silica gel with PhH–hexane (70:30) as the eluent. The pure product melted at 82° (lit.[18] mp 81–82°).

2,4,5-Tribenzyloxybenzaldehyde was prepared by a modification of the published procedure.[18] A mixture of 5 ml of DMF and 3.1 g of $POCl_3$ (0.02 mole) were stirred at room temperature for 30 min. Carefully dried 1,2,4-tribenzyloxybenzene (3.96 g, 0.01 mole) was then added and the mixture was stirred and heated at 80° for 3 hr under anhydrous conditions. After addition of ice and filtration, the precipitate was extracted (EtOAc). The extract was washed with dilute Na_2CO_3 and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the product was recrystallized from PhH–hexane to yield 3.43 g (81%) of aldehyde, mp 133–134° (lit.[18] mp 132–133°).

2,4,5-Tribenzyloxybenzyl Alcohol (I).—To 1.3 g of LAH, suspended in 10 ml of THF under N_2, was slowly added 1.5 g of 2,4,5-tribenzyloxybenzaldehyde in 8 ml of THF. The mixture was stirred, refluxed for 3 hr, and cooled, and 1.3 ml of H_2O, 1.3 ml of 15% NaOH, and, finally, 3.9 ml of H_2O were added. The granular precipitate was removed by filtration and washed several times with hot THF. The combined filtrate and washings were dried (Na_2SO_4) overnight. After evaporation of the solvent, white crystals remained, weighing 1.2 g (80%); after recrystallization with cyclohexane: mp 115–116°; $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3400 (OH); nmr ($CHCl_3$), δ 4.60 (1, OH), 4.98 (2, OCH_2Ar), 5.10 (4, OCH_2Ar), 6.63 (1, aromatic H), 6.95 (1, aromatic H), 7.36 (15, aromatic H). *Anal.* ($C_{28}H_{26}O_4$) C, H.

2,4,5-Tribenzyloxybenzyl Bromide (II).—To a cooled, stirred solution of 0.5 g of fresh PBr_3 in 5 ml of CCl_4 was slowly added, 250 mg of carefully dried 2,4,5-tribenzyloxybenzyl alcohol. The mixture was stoppered tightly and allowed to stand in the dark for 5 hr. The slightly yellowish solution was then refluxed briefly for 15 min, cooled, and poured over 20 g of crushed ice. The organic layer was separated, and washed with ice-cold $NaHCO_3$ until the washings were almost neutral to litmus. After drying (Na_2SO_4) and evaporation *in vacuo* at 40°, a colorless oil was obtained which, upon chilling and scratching, solidified to rhombic crystals. Recrystallization from boiling hexane gave 220 mg (80%) of pure II: mp 88–89°; nmr ($CDCl_3$), δ 4.50 (2, CH_2Br), 4.98 (2, CH_2Ar), 5.04 (4, OCH_2Ar), 6.55 (1, aromatic H), 6.95 (1, aromatic H), 7.36 (15, aromatic H). *Anal.* ($C_{28}H_{25}BrO_3$) C, H, Br.

Dibenzyl carbobenzyloxyaminomalonate was prepared by the method of Kissman and Witkop.[19] Dibenzyl malonate was nitrosated, reduced with Al–Hg, and acylated with benzyl chlorocarbonate in C_6H_6 in the presence of K_2CO_3. The over-all yield of product based upon dibenzyl malonate was 35%. It melted at 109° (lit.[19] mp 111–112°).

Dibenzyl Carbobenzyloxyamino(2,4,5-tribenzyloxybenzyl)-malonate (III).—To a solution of 0.433 g (0.001 mole) of dibenzyl carbobenzyloxyaminomalonate in 8 ml of anhydrous PhMe was added 58 mg of a NaH slurry (53% in mineral oil, 0.0013 mole) under N_2. The mixture was heated and stirred at 100° until the gas evolution had subsided (30 min). 2,4,5-Tribenzyloxybenzyl bromide (528 mg) was added and the mixture was refluxed for an additional 18 hr. The chilled mixture was poured over ice and the organic layer was separated and dried (Na_2SO_4) overnight. After evaporation of the solvent *in vacuo*, a viscous mass was obtained which, by tlc examination (silica GF 253, $CHCl_3$), contained a number of products. The major product, III, was purified by tlc. An analytical sample was prepared by repeated tlc. Attempts to crystallize this compound were unsuccessful; $\nu_{max}^{CHCl_3}$ (cm^{-1}) 3400 (NH), 1740 ($COOCH_2C_6H_5$), 1710 ($COOCH_2C_6H_5$); nmr ($CDCl_3$), δ 3.70 (2, CH_2Ar), 4.95 (12, OCH_2Ar), 6.53 (1, aromatic H), 6.90 (1, aromatic H), 7.31 (30, aromatic H). *Anal.* ($C_{53}H_{47}NO_9$) C, H, N.

Diethyl formamido(2,4,5-tribenzyloxybenzyl)malonate (IV) was prepared in a similar manner, using 2,4,5-tribenzyloxybenzyl bromide, diethyl formamidomalonate (10% excess), and NaH. After working up the reaction mixture as described above, a crystalline product was obtained in 65% yield; mp 109°; ν_{max}^{Nujol} (cm^{-1}) 3300 (NH), 1730 (COOEt), 1650 (CONH); nmr ($CDCl_3$), δ 1.10 (6, CH_3), 3.60 (2, CH_2Ar), 4.00 (4, OCH_2), 4,85 (2, OCH_2Ar), 5.04 (4, OCH_2Ar), 6.50 (1, aromatic H), 6.90 (1, aromatic H), 7.36 (15, aromatic H). *Anal.* ($C_{36}H_{37}NO_8$) C, H.

Diethyl acetamido(2,4,5-tribenzyloxybenzyl)malonate (V) was prepared in the same manner in 60% yield. The product, which melted at 115–116°, was recrystallized from PhH–petroleum ether; ν_{max}^{Nujol} (cm^{-1}) 3300 (NH) 1720 (COOEt), 1640 (CONH); nmr ($CDCl_3$), δ 1.10 (6, CH_3), 2.2 (3, $COCH_3$), 3.65 (2, CH_2Ar), 4.05 (4, OCH_2), 4.90 (2, OCH_2Ar), 5.10 (4, OCH_2Ar), 6.52 (1, aromatic H), 6.95 (1, aromatic H), 7.39 (15, aromatic H).

2,4,5-Trihydroxyphenylalanine (6-Hydroxydopa) (VII).—A slow stream of H_2 was bubbled through a suspension of 150 mg of 10% Pd–C in 20 ml of EtOH containing 172 mg (0.2 mmole) of III and 0.2 ml of 2 *N* HCl. After 4 hr, the catalyst was filtered off. The filtrate was concentrated *in vacuo* at 40% to yield a yellowish residue. Dissolving this material in MeOH, followed by reprecipitation with Et_2O, gave a very hygroscopic solid which darkened rapidly upon exposure to air. Tlc (silica gel GF 253, *n*-BuOH–AcOH–H_2O, 4:1:1) revealed essentially one major product with an R_f value of 0.32 and a minor product at R_f 0.50. The former compound (brownish coloration with ninhydrin) was apparently the dibasic amino acid, amino(2,4,5-trihydroxybenzyl)malonic acid hydrochloride (VI), while the latter (purple coloration with ninhydrin) was the desired 2,4,5-trihydroxyphenylalanine (VII). Both gave brown coloration with Gibbs' reagent.[20]

In order to effect complete decarboxylation, 31 mg of reprecipitated VI (crude material could not be used) was dissolved in 10 ml of EtOH and heated under N_2 for 5 min. After evaporation of the solvent *in vacuo*, a white precipitate (21 mg, 80%) remained which showed only one spot (R_f 0.50) on silica gel GF 253 plates (*n*-BuOH–AcOH–H_2O, 4:1:1). This compound was further characterized VII by mass spectroscopy (*m/e* 214 = M + 1, 168 = M − COOH) and by decarboxylation to 6-hydroxydopamine (see below). *Anal.* ($C_9H_{12}ClNO_5$) N.

2-Phenyl-5-(2,4,5-trimethoxybenzal)oxazolone (VIII).—2,4,5-Trimethoxybenzaldehyde (1 g, 5.1 mmoles), 1 g of hippuric acid (5.6 mmoles), 0.5 g of fused NaOAc, and 4 ml of Ac_2O were heated at 110° for 6 hr. Ice was added to the deep orange mixture and the product was removed by filtration or decantation. Recrystallization from C_6H_6–hexane gave 1.48 g (87%) of orange-red prisms: mp 205°; ν_{max}^{Nujol} (cm^{-1}) 1750 (lactone carbonyl), 1620 (C=N); λ_{max}^{EtOH} 440 mμ (ϵ 19,000). *Anal.* ($C_{19}H_{17}NO_5$) C, H, N.

α-Benzamido(2,4,5-trimethoxy)cinnamic Acid (IX).—2-Phenyl-5-(2,4,5-trimethoxybenzal)oxazolone (0.5 g, 1.47 mmoles) was refluxed with 16 ml of 0.1 *N* NaOH until the solution was almost clear (3 hr). The mixture was filtered and chilled well before being acidified (pH 2) with 10% ice-cold HCl. The slightly yellowish solid was isolated by filtration and air dried. Recrystallization from boiling EtOH afforded 432 mg (86%) of pale yellow needles: mp 223–224° dec; ν_{max}^{Nujol} (cm^{-1}) 1675 (COOH, α,β unsaturated), 1640 (CONH); mass spectrum, *m/e* 357 = M, 313 = M − CO_2. *Anal.* ($C_{19}H_{19}O_6$) C, H, N.

N-Benzamido(2,4,5-trimethoxyphenyl)alanine (X).—A suspension of 150 mg of α-benzamido-2,4,5-trimethoxycinnamic acid,

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0.5 g of *d*-limonene, and 10 ml of *n*-AmOH was heated under reflux under N_2 for 18 hr.[21] The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to dryness. Crystallization of the residue from $CHCl_3$–hexane gave 123 mg (82%) of a white, amorphous solid: mp 186–187°; ν_{max}^{Nujol} (cm^{-1}) 3250 (OH), 1700 (COOH), 1635 (CONH); mass spectrum *m/e* 359 = M.

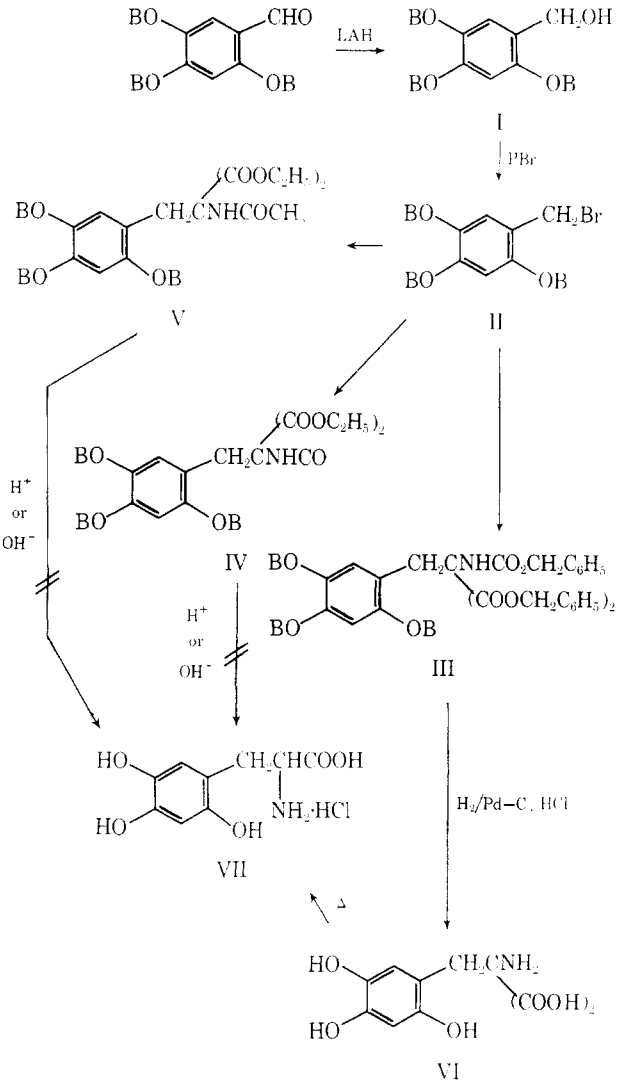
Enzymatic Decarboxylation of 2,4,5-Trihydroxyphenylalanine (6-Hydroxydopa).—Aromatic amino acid decarboxylase was purified through the first ammonium sulfate precipitation from guinea pig kidney by the method of Clark, *et al.*[22] The reaction mixture contained the following components (in micromoles): phosphate buffer, pH 6.2, 500; pyridoxal phosphate, 10; 6-hydroxydopa, 10; and 0.7 ml of the decarboxylase preparation containing 12 mg of protein, in a final volume of 1.0 ml. The reaction was carried out under N_2 for 30 min at 37°. Protein was precipitated with EtOH (2 ml) and removed by centrifugation, and the supernatant was lyophilized. The residue was dissolved in 0.01 *N* HCl and applied to a micro Dowex 50 H^+ column (2 × 0.5 cm), washed with 0.01 *N* HCl, and the amino acid and amine were eluted with 2 *N* HCl (6 ml). After lyophilization, paper chromatography (HCO_2H–*sec*-BuOH–H_2O, 15:75:10) ($C_5H_5NO_2$–AcOH–H_2O, 90:28:12), and tlc ($C_5H_5NO_2$–AcOH–H_2O, 90:28:12 on alumina), R_f values for 6-hydroxydopamine and 6-hydroxydopa in these systems were 0.24, 0.15; 0.13, 0.05; and 0.12, 0.45, respectively. The compounds were visualized with $K_3Fe(CN)_6$ in phosphate buffer, pH 7.5, which yields characteristic red spots. No product formation was observed in the absence of pyridoxal phosphate or when heat-denatured enzyme was employed. Comparison to results obtained using L-DOPA as substrate indicated that a nearly equivalent rate of decarboxylation was obtained with 6-hydroxydopa.

Results and Discussion

The synthesis of 2,4,5-trihydroxyphenylalanine (VII, 6-hydroxydopa) proved to be difficult by the conventional procedures of amino acid synthesis which involve the use of diethyl acetamido- or diethyl formamidomalonate. Attempts using various acidic and basic conditions to remove the blocking groups from the diethyl acetamido- or diethyl formamido(2,4,5-tribenzyloxybenzyl)malonate (V, IV) and to bring about decarboxylation resulted in a complex mixture of products. A successful approach (Scheme I) was found to involve the use of dibenzyl N-carbobenzyloxyaminomalonate,[10,23] whereby the benzyl and carbobenzyloxy blocking groups could be removed from the dibenzyl carbobenzyloxyamino(2,4,5-tribenzyloxybenzyl)malonate (III) under mild conditions of hydrogenolysis. Thermal decarboxylation of VI in EtOH then led smoothly to 2,4,5-trihydroxyphenylalanine (6-hydroxydopa) (VII). An alternate approach (Scheme II) was explored in the synthesis of N-benzoyl-2,4,5-trimethoxyphenylalanine (X). In this case, attempted generation of VII under acidic conditions led to a complex mixture of products. Limonene and Pd–C were employed as reducing agents, since they do not cleave benzyl ethers,[21] and it was originally planned to extend this approach to the 2,4,5-tribenzyloxy series.

The formation during melanogenesis of a compound with chromatographic properties that might be expected of 2,4,5-trihydroxyphenylalanine (VII) has been reported.[24,25] In addition, the synthesis of 2,4,5-trihydroxyphenylalanine has been mentioned by Swan.[26] No

Scheme I



details or properties of the substance were reported except that the compound gave lower yields of melanin-like material than either dopamine or dopa. Thus the present procedure seems to be the first report of a satisfactory method of synthesizing the quantities of 6-hydroxydopa required for pharmacological studies.

6-Hydroxydopa was found to cause release of norepinephrine from cardiac tissue using the technique of prelabeling the norepinephrine stores with tracer amounts of norepinephrine-^{3}H.[17] As presented in Table I, 6-hydroxydopa caused a significant release of norepinephrine-^{3}H from cardiac tissue during the 2-hr period of the assay. The effective dose for 50% release of norepinephrine-^{3}H was found to be 100 mg/kg. For comparison, the ED_{50} of other amino acids that are norepinephrine-depleting agents, such as α-methyl-*m*-tyrosine and 3,5-dihydroxy-4-methoxyphenylanine are, respectively, 9[27] and 31 mg/kg.[28] That 6-hydroxydopa does not release norepinephrine-^{3}H *per se* was shown by concomitant use of the decarboxylase inhibitor, N-DL-seryl-2,3,4-trihydroxybenzylhydrazine.[29] Employing the technique of Creveling, *et al.*,[27,28] it was found that 6-hydroxydopa caused essentially no release of norepi-

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SCHEME II

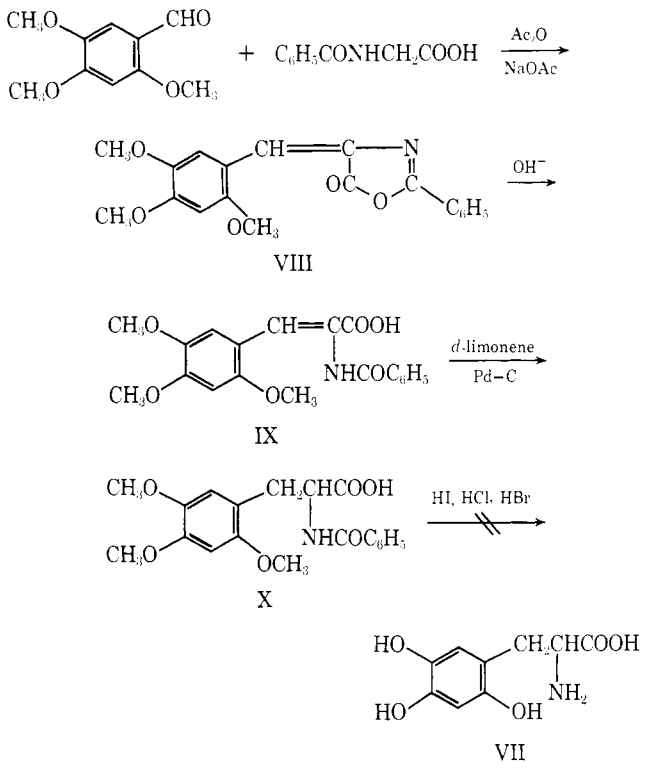

TABLE I

THE DEPLETION OF NOREPINEPHRINE IN MOUSE HEART AND BRAIN BY 6-HYDROXYDOPA

Compound	Dose, mg/kg	Heart[a] (% of control)	Brain,[b] μg/g
6-Hydroxydopa	50	63	0.27
	100	51	0.24
6-Hydroxydopa (plus decarboxylase inhibitor)[c]	200	43	0.16
	100	94	0.12
6-Hydroxydopamine			
6-Hydroxydopamine (plus decarboxylase inhibitor)[c]	5	42	0.36
	5	45	0.38
Control			0.35 ± 0.02

[a] Assay as described for chemorelease of norepinephrine-^{3}H[16] with five mice per group; time, 2 hr. Standard error ±7%. HCl salts were used. [b] See Table II. Time, 2 hr. [c] The peripheral decarboxylase inhibitor N-DL-seryl-N′-2,3,4-trihydroxybenzylhydrazine (50 mg/kg ip) was given 30 min before 6-hydroxydopa or 6-hydroxydopamine.

nephrine-^{3}H when the action of aromatic amino acid decarboxylase was blocked by the inhibitor (Table I). This is convincing evidence that, as is the case with other amino acids,[30] prior decarboxylation of 6-hydroxydopa is required for norepinephrine release. *In vitro* studies (see Experimental Section) indicate that 6-hydroxydopa is readily decarboxylated to 6-hydroxydopamine by mammalian aromatic amino acid decarboxylase.

Endogenous norepinephrine in brain[31] was reduced to 60% of control levels following the administration of 100 mg/kg of 6-hydroxydopa (Table II). This depletion persisted for at least 3 days. Occasional toxic effects were observed in mice receiving higher doses of 6-hydroxydopa and slightly greater depletion of central norepinephrine was effected. 6-Hydroxydopa (50–200 mg/kg) produced a syndrome similar in some respects to that caused by reserpine. The mice were less active and exhibited a typical "hunched-back" posture, mincing gait, and a distinct tremor.

TABLE II

DEPLETION OF BRAIN NOREPINEPHRINE BY 6-HYDROXYDOPA

Time, hr	Norepinephrine, μg/g[a] 6-Hydroxydopa[b]	Norepinephrine, μg/g[a] 6-Hydroxydopa[b] (peripheral decarboxylase inhib)[c]
2	0.24 ± 0.04	0.11 ± 0.01
5	0.25 ± 0.05	0.14 ± 0.02
24	0.23 ± 0.02	0.31 ± 0.02
48	0.19 ± 0.02	0.27 ± 0.03
72	0.24 ± 0.01	0.35 ± 0.03
Control	0.35 ± 0.02	0.36 ± 0.02

[a] Assay[31] on three to five groups of five mice (16–20-g male white NIH general purpose). [b] 100 mg/kg sc. [c] N-DL-Seryl-N′-2,3,4-trihydroxybenzylhydrazine (50 mg/kg ip) administered 30 min before and 30 min after 6-hydroxydopa.

Depletion of norepinephrine in the brain to a level of less than 30% of control was brought about by the administration of a peripheral decarboxylase inhibitor, N-DL-seryl-N′-2,3,4-trihydroxybenzylhydrazine (50 mg/kg), 30 min prior to the subcutaneous administration of 100 mg/kg of 6-hydroxydopa. This technique has been used previously to inhibit selectively peripheral aromatic amino acid decarboxylase and thereby cause increased uptake of dopa into the central nervous system where it is decarboxylated to dopamine.[32,33] Although the depletion of endogenous norepinephrine in the brain was greater when 6-hydroxydopa and a peripheral decarboxylase inhibitor were used together, the norepinephrine levels returned to normal more rapidly than when 6-hydroxydopa was used alone (Table II). The reason for this is not known.

Further studies will be needed to determine whether selective destruction of adrenergic nerve terminals can be effected in the CNS with 6-hydroxydopa. The results reported here only indicate that this amino acid can partially reduce the level of norepinephrine in the whole brain, a reduction which is enhanced in the presence of a peripheral decarboxylase inhibitor. The depletion of norepinephrine and concomitant reserpine-like syndrome persists only for a few days in these mice, which suggests an impairment of nerve function rather than destruction of the nerve terminals. It is noteworthy that the reserpine-like syndrome is elicited when norepinephrine is only partially depleted (greater than 50% of control) which suggests that 6-hydroxydopa may have a greater affinity for certain regions of the CNS and produce a more extensive depletion of specific norepinephrine-containing nerves.[34]

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(34) While this manuscript was in preparation, Dr. H. Thoenen, F. Hoffman-La Roche & Co. Ltd., Basle, informed the authors of essentially similar results obtained with 6-hydroxydopa in rats.