lytical samples of the phthalimidobutyl- and the phthalimidohexylglutathiones were prepared by recrystallization from ethanol-water. The phthalimidooctyl- and phthalimidodecylglutathiones were recrystallized from DMF-water.

S-(ω-Aminoalkyl)glutathiones. Hydrazinolysis of the phthalimido group was effected by the addition of 0.02 mol of 95% hydrazine to 0.01 mol of the phthalimido-substituted compound dissolved in 50 ml of DMF-water (50:50). The resulting solution was allowed to stir for 2 days at room temperature, by which time the solution had become quite turbid. After neutralization with concentrated HI the suspension was chilled, and the phthalhydrazide was removed by high-speed centrifugation. The supernatant portion was concentrated *in vacuo* to a low volume, and an additional volume of water was added. After chilling, more phthalhydrazide precipitated and was removed by filtration. The filtrate was then concentrated to very low volume, and the final product was crystallized from solution by the addition of ethanol. The hygroscopic solid was removed by filtration, washed with ethanol, and dried in a heated vacuum desiccator in the presence of phosphorus pentoxide. The final products gave a single ninhydrin spot in the solvent system above. Analytical samples were prepared by first dissolving the products in a minimum volume of hot water and then effecting crystallization by the addition of ethanol.

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Action of (*S*)- and (*R*)-Para-Substituted Amphetamine Hydrochlorides and (α*S*)- and (α*R*)-*p*-Chloronorephedrine and (α*S*)- and (α*R*)-*p*-Chloronorpseudoephedrine Hydrochlorides on the Level of 5-Hydroxytryptamine and the Activity of Tryptophan Hydroxylase in Rat Brain†,‡

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Both (*S*)-(+)- and (*R*)-(−)-*p*-chloroamphetamine hydrochloride cause a reduction in the level of 5-hydroxytryptamine (serotonin, 5-HT) and the activity of tryptophan hydroxylase in rat brain. The *R* isomer induces a more rapid decline in 5-HT which is of shorter duration. The effect of this isomer on tryptophan hydroxylase activity disappeared 2 weeks after injection, but the effect of the *S* isomer persisted. These results indicate that different mechanisms are involved in the short- and long-term effects. (*S*)-(+)- and (*R*)-(−)-*p*-nitroamphetamine hydrochloride both reduce 5-HT levels and tryptophan hydroxylase activity 4 hr after injection, with some recovery after 2 weeks. Since (α*S*)-(−)- and (α*R*)-(+)-*p*-chloronorephedrine hydrochloride and (α*S*)-(+)- and (α*R*)-(−)-*p*-chloronorpseudoephedrine hydrochloride do not have a significant effect on the level of 5-HT or the activity of tryptophan hydroxylase, β-hydroxylation is not an important factor in either the short- or long-term effects of *p*-chloroamphetamine hydrochloride on serotonergic neurons.

The administration of racemic *p*-chloroamphetamine hydrochloride [(±)-1a] to rats leads to a marked and long-lasting reduction of the levels of 5-hydroxytryptamine (serotonin, 5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) and the activity of tryptophan hydroxylase in the brain.[2] Although some recovery is observed, all three components are still significantly reduced 4 months after a single injection of (±)-1a. Tryptophan hydroxylase activity *in vitro*, however, was unaffected by addition of the racemic drug.[3]

Since it is known that enantiomers of a drug can produce different pharmacological effects,[4] we have now compared the effect of (*S*)-(+)- and (*R*)-(−)-*p*-chloroamphetamine hydrochloride§,[6] [(*S*)-1a and (*R*)-1a] on the

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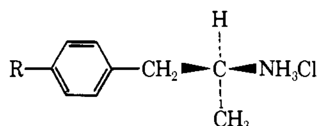
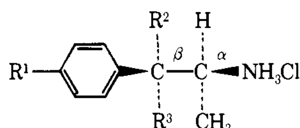
‡Taken in part from the M.S. Thesis of C. D. M., Tennessee State University, May 1973.



(*S*)-**1a**, R = Cl
(*S*)-**2a**, R = H
(*S*)-**3a**, R = CH_3CO
(*S*)-**4a**, R = NO_2
(*S*)-**5a**, R = NH_3Cl



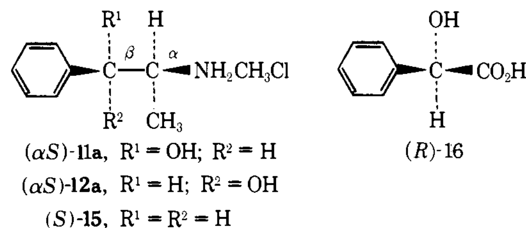
(α*S*)-**6a**, R^1 = Cl; R^2 = OH; R^3 = H
(α*S*)-**7a**, R^1 = Cl; R^2 = H; R^3 = OH
(*S*)-**8a**, R^1 = OH; R^2 = R^3 = H
(α*S*)-**9a**, R^1 = R^2 = OH; R^3 = H
(α*S*)-**10a**, R^1 = OH; R^2 = H; R^3 = OH
(α*S*)-**13a**, R^1 = H; R^2 = OH; R^3 = H
(α*S*)-**14a**, R^1 = R^2 = H; R^3 = OH

levels of 5-HT and the activity of tryptophan hydroxylase in rat brain. This seemed especially important in view of the report that only one enantiomer of *p*-acetyldeoxyephedrine hydrochloride (*N*-methyl derivative of **3a**) was active in lowering levels of 5-HT in mice brain.[7] Not only was (*S*)-*p*-acetyldeoxyephedrine hydrochloride ineffective, but it blocked the effect of its enantiomer when both were administered together.[7]

In order to assess the generality of the consequences of a substituent at the para position of amphetamine, we have also examined the effect of (*S*)-(+)- and (*R*)-(−)-*p*-nitroamphetamine hydrochloride[8] [(*S*)-**4a** and (*R*)-**4a**] and (*S*)-(+)- and (*R*)-(−)-*p*-aminoamphetamine dihydrochloride[9] [(*S*)-**5a** and (*R*)-**5a**] on 5-HT levels and tryptophan hydroxylase activity in rat brain.

The finding that (±)-*p*-chloroamphetamine hydrochloride [(±)-**1a**] inhibits the activity of tryptophan hydroxylase *in vivo* but not *in vitro*[3] suggests the possibility of the formation of an active metabolite of (±)-**1a** *in vivo*. The metabolic pattern of (*S*)-(+)-amphetamine [(*S*)-**2b**] in rats[10-12] and the observation that (±)-**1a** is a substrate for dopamine β-hydroxylase‡ suggest one of the enanthiomers of *p*-chloronorephedrine (**6b**) or *p*-chloronorpseudoephedrine (**7b**) as a likely candidate for such a metabolite. In rats, (*S*)-**2b** is metabolized to (*S*)-*p*-hydroxyamphetamine [(*S*)-**8b**], which is subsequently converted by dopamine β-hydroxylase to a metabolite identified as *p*-hydroxynorephedrine.[12] This metabolite has been implicated in the persistent reduction of brain norepinephrine after the administration of (*S*)-**2b** to rats.[10,11,13] The absolute configuration of (*S*)-**8b** follows from the known absolute configuration of its precursor,[14] (*S*)-**2b**, but it has not been established whether the major metabolite of (*S*)-**8b** is (α*S*)-*p*-hydroxynorephedrine [(α*S*)-**9b**] or (α*S*)-*p*-hydroxynorpseudoephedrine [(α*S*)-**10b**].

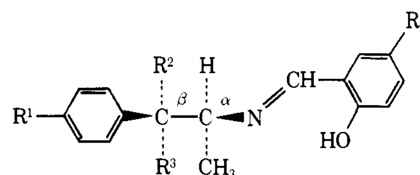
In order to ascertain the possible role of an enantiomer of *p*-chloronorephedrine [(α*S*)-**6b** or (α*R*)-**6b**] or of *p*-chloronorpseudoephedrine [(α*S*)-**7b** or (α*R*)-**7b**] as an active metabolite of (±)-*p*-chloroamphetamine, we have synthesized the respective hydrochlorides as their racemic modifications[15,16] and have examined the effects of (α*S*)-(−)- and (α*R*)-(+)-*p*-chloronorephedrine hydrochloride [(α*S*)-**6a** and (α*R*)-**6a**] and (α*S*)-(+)- and (α*R*)-(−)-*p*-chloronorpseudoephedrine hydrochloride [(α*S*)-**7a** and (α*R*)-**7a**], obtained by resolution of the racemates, on the levels of 5-HT and the activity of tryptophan hydroxylase in rat brain.



(α*S*)-**11a**, R^1 = OH; R^2 = H
(α*S*)-**12a**, R^1 = H; R^2 = OH
(*S*)-**15**, R^1 = R^2 = H
(*R*)-**16**

The relative configurations of (±)-**6a** and (±)-**7a** were assigned earlier[16] by their mode of synthesis and are now confirmed by comparison of their pmr spectra with those of (α*S*)-ephedrine [(α*S*)-**11b**], (α*S*)-pseudoephedrine [(α*S*)-**12b**], (±)-norephedrine hydrochloride [(±)-**13a**], and (α*S*)-(+)-norpseudoephedrine hydrochloride [(α*S*)-**14a**]. The absolute configurations of these models are known in that (α*S*)-(−)-norephedrine hydrochloride [(α*S*)-**13a**] has been related to (α*S*)-(−)-ephedrine hydrochloride [(α*S*)-**11a**][17] and (α*S*)-(+)-norpseudoephedrine hydrochloride [(α*S*)-**14a**] to (α*S*)-(+)-pseudoephedrine hydrochloride [(α*S*)-**12a**].[18] Both (α*S*)-**11a** and (α*S*)-**12a** have been converted to (*S*)-(+)-deoxyephedrine hydrochloride [(*S*)-**13**],[19] which has been prepared from (*S*)-(+)-amphetamine hydrochloride [(*S*)-**2a**].[20] (α*S*)-**11a** has also been obtained from (*R*)-mandelic acid[21] [(*R*)-**16**] and (α*S*)-**12a** from (*S*)-**16**.[20]

The absolute configurations of the optically pure *p*-chloronorephedrine and *p*-chloronorpseudoephedrine hydrochlorides were established by preparation of the Schiff bases, (α*S*)-(+)-*N*-(5-bromosalicylidene)-*p*-chloronorephedrine [(α*S*)-**6c**] and (α*S*)-(+)-*N*-(5-bromosalicylidene)-*p*-chloronorpseudoephedrine [(α*S*)-**7c**], and application of the *N*-salicylidene sector rule[22] to an interpretation of their respective CD spectra. Examination of the CD spectra of the *N*-5-bromosalicylidene derivatives (*R*)-**1c**, (*S*)-**2c**,[23] (α*R*)-**13c**, and (α*S*)-**14c** and the *N*-salicylidene derivatives (*S*)-**2d**[23] and (α*S*)-**14d**, prepared from the respective amines, affirms the validity of the sector rule and the utility of *N*-5-bromosalicylidene derivatives.



(*S*)-**1c**, R^1 = Cl; R^2 = R^3 = H; R^4 = Br
(*S*)-**2c**, R^1 = R^2 = R^3 = H; R^4 = Br
(*S*)-**2d**, R^1 = R^2 = R^3 = R^4 = H
(α*S*)-**6c**, R^1 = Cl; R_2 = OH; R^3 = H; R^4 = Br
(α*S*)-**7c**, R^1 = Cl; R^2 = H; R^3 = OH; R^4 = Br
(α*S*)-**13c**, R^1 = H; R^2 = OH; R^3 = H; R^4 = Br
(α*S*)-**14c**, R^1 = R^2 = H; R^3 = OH; R^4 = Br
(α*S*)-**14d**, R^1 = R^2 = H; R^3 = OH; R^4 = H

Results and Discussion

Synthesis. (*S*)-(+)- and (*R*)-(−)-*p*-nitroamphetamine hydrochlorides [(*S*)-**4a** and (*R*)-**4a**] were obtained by crys-

§Signs in parentheses refer to rotatory powers observed with sodium D light for the amine hydrochlorides in water and for the amines and Schiff bases in absolute ethanol. It is to be noted that (*S*)-(+)-amphetamine hydrochloride [(*S*)-2a] is dextrorotatory in water and levorotatory in absolute ethanol.[5]

‡C. Brown, University of Tennessee School of Medicine, personal communication, 1973.

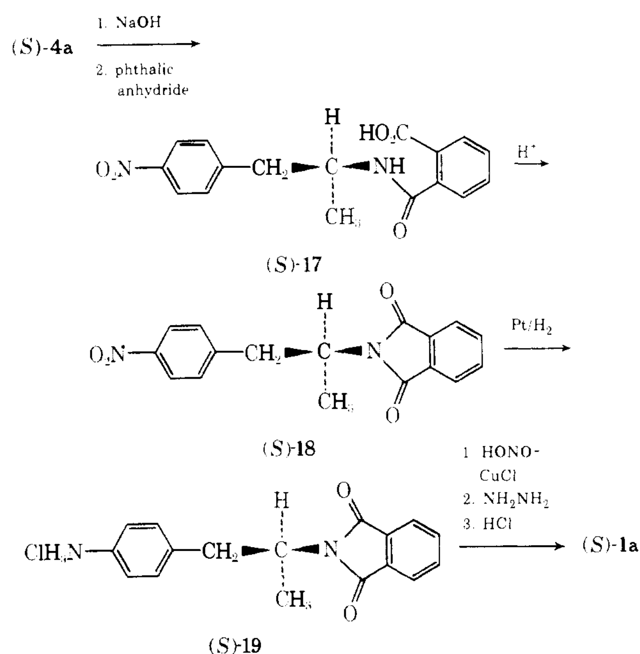
Table I. Pmr Data for Ephedrine and Related Compounds[a]

Compd	δ,[b] ppm (*J*, Hz)		
	αC-H[c]	βC-H[d]	C-CH$_3$[d]
(±)-**6a**	3.60	5.10 (3.5)	1.12 (7.0)
(±)-**7a**	3.50	4.58 (8.0)	1.10 (7.0)
(αS)-**11b**[e]	3.54	5.62 (4.0)	1.82 (6.0)
(αS)-**12b**[e]	3.55	4.25 (8.2)	1.70 (7.0)
(±)-**13a**	3.55	5.11 (4.0)	1.15 (7.0)
(αS)-**14a**	3.50	4.65 (9.0)	1.12 (7.0)

[a]Hydrochlorides in CD_3OD and free bases in $CDCl_3$. [b]Downfield from TMS. [c]Multiplet. [d]Doublet. [e]Data from ref 24.

tallization of the hydrochlorides resulting from nitration of (*S*)-2a and of (*R*)-**2a**.[8] Catalytic hydrogenation of (*S*)-**4a** and (*R*)-4a gave (*S*)-**5a** and (*R*)-**5a**,[9] respectively. (*S*)-4a was also converted in two steps to (*S*)-*N*-phthaloyl-*p*-nitroamphetamine [(*S*)-**18**, Scheme I], which was hydrogenated to (*S*)-*N*-phthaloyl-*p*-aminoamphetamine hydrochloride [(*S*)-**19**]. Diazotization of (*S*)-**19** followed by hydrazinolysis yielded (*S*)-(+)-*p*-chloroamphetamine hydrochloride [(*S*)-1a]. The conversion (*S*)-2a to (*S*)-1a confirms the earlier assignment[6] of the *S* configuration to the dextrorotatory isomer of **1a.** (*R*)-1a was obtained by resolution of (±)-1a as its *N*-acetyl-L-leucinate salt.[6]

Scheme I



(±)-*p*-Chloronorephedrine hydrochloride[15,16] [(±)-6a] was synthesized in three steps from 4′-chloropropiophenone (see Experimental Section). Inversion of configuration at the β-carbon atom by treatment of the *N*-acetyl derivative of (±)-6a with thionyl chloride followed by aqueous alkali produced (±)-7a.[16] (±)-**6a** was resolved using *N*-acetyl-L- and *N*-acetyl-D-leucine, while the enantiomers of (±)-7a were supplied to us by Dr. J. Lafferty, Smith Kline & French Laboratories.

Configurational Studies. The pertinent pmr data for (±)-*p*-chloronorephedrine hydrochloride [(±)-6a] and (±)-*p*-chloronorpseudoephedrine hydrochloride [(±)-7a] are compared with those of the model compounds in Table I. As has been discussed in detail in the case of the diastereomeric ephedrines (α*R*)-**11b** and (α*S*)-**12b**,[24] the erythro configuration produces a coupling constant for the interaction of the α and β protons about one-half as great as does the threo configuration. Similar coupling constants are observed for (±)-**13a** and (α*S*)-**14a**, erythro and threo, respectively. Thus, (±)-**6a** and (±)-**7a** have these same respective relative configurations.

The CD data for the Schiff bases are summarized in Table II. As reported earlier for (*S*)-(+)-*N*-salicylidenamphetamine[22] [(*S*)-**2d**], strong positive Cotton effects near 255 and 315 nm correlate with the *S* configuration. The CD spectrum of (*S*)-**2c** indicates that the same is true for the *N*-5-bromosalicylidene derivative. The spectrum of (*R*)-**1c** as compared to (*S*)-**2c** indicates also no significant change due to the *p*-chloro substituent on the amine moiety. Also, the observed spectra for (α*R*)-**13c**, (α*S*)-**14c**, and (α*S*)-**14d** confirm that the configuration of the contiguous asymmetric center in these norephedrine derivatives has an insignificant effect on the observed Cotton effects near 255 and 315 nm, the sign of these Cotton effects being determined only by the configuration of α-carbon atom. Thus, (−)-*p*-chloronor- and (+)-*p*-chloronorpseudoephedrine hydrochloride are each assigned the α*S* configuration on the basis of the CD spectra of their respective *N*-5-bromosalicylidene derivatives.

Biological Activity. The activity of tryptophan hydroxylase and the levels of 5-hydroxytryptamine (5-HT) in brain were determined in animals killed 4 hr or 2 weeks after injection of the β-phenylethylamine derivatives (Table III). In agreement with earlier reports,[25,26] both optical isomers of *p*-chloroamphetamine hydrochloride (1a) reduce the level of brain 5-HT. The activity of tryptophan hydroxylase is also significantly reduced 4 hr after injection of both isomers. However, the long-term effects of the two isomers are different. (*R*)-1a induces a more rapid decline in brain 5-HT which is of shorter duration. Moreover, the effect of (*R*)-1a on tryptophan hydroxylase activity has disappeared 2 weeks later, while the effect of (*S*)-1a persists. These results indicate that the mechanism of the long-term reduction of the level of 5-HT and the activity of tryptophan hydroxylase after the administration of (±)-1a must be different from the mechanism of the early effects.

As discussed previously, it seemed possible that the β-hydroxylated metabolite, *p*-chloronorephedrine, might be responsible for the long-term effects of (±)-1a and particularly of (*S*)-1a. An investigation of all four isomers of the β-hydroxylated compound [(α*S*)-**6a**, (α*R*)-6a, (α*S*)-**7a**, and (α*R*)-7a] showed, however, that they do not decrease the levels of 5-HT in brain, either at 4 hr or 2 weeks after a large dose. The activity of tryptophan hydroxylase was also not appreciably changed, except for a slight decrease 2 weeks after injection of (α*S*)-**6a**. Furthermore, the reduction of tryptophan hydroxylase activity by (±)-**1a** is not prevented by pretreatment with disulfiram, which inhibits dopamine β-hydroxylase[27] and should block the *in vivo* formation of a β-hydroxylated metabolite. Four hours after the intraperitoneal injection of 10 mg/kg of (±)-1a, the activity of tryptophan hydroxylase in brains of rats pretreated with disulfiram (500 mg/kg ip) was reduced by 34 ± 4%, while that in brains of rats pretreated with saline was reduced by 50 ± 3%. Therefore, it appears that β-hydroxylation of either isomer of **1a** is not critical for either its short- or long-term effects on serotonergic neurons.

Both optical isomers of *p*-nitroamphetamine hydrochloride (4a) induce a depletion of 5-HT and a decrease in tryptophan hydroxylase activity within 4 hr. Although considerable recovery occurs in both the levels of the amine and the activity of the enzyme, a significant decrease is still evident 2 weeks later. (*S*)-(+)-*p*-Aminoam-

Table II. EA and CD Spectral Data for Schiff Bases in Absolute Ethanol[a]

		CD			
Compd	EA max, λ, nm (ε[c])	Longest and shortest λ, nm ([θ][b])	Max, λ, nm ([θ][b])	Min, λ, nm ([θ][b])	[θ][b] = ±0, λ, nm[d]
(*R*)-**1c**		500 (±0)			455
	415 (600)		415 (−1,500)	380 (−900)	
	328 (3,700)		326 (−14,000)	280 (−900)	
	276 (1,700)[e]				
	254 (10,000)[e,f]		255 (−43,000)		237
		233 (+2,200)			
(*S*)-**2c**		500 (±0)			470
	415 (740)		411 (+2,200)	370 (+1,100)	
	327 (3,600)		327 (+12,000)	277 (+1,000)	
	276 (1,600)[e]				
	254 (10,000)[e]		254 (+35,000)		237
		233 (−8,200)			
	220 (31,000)				
(*S*)-**2d**		500 (±0)			460
	403 (630)		399 (+1,700)	363 (+1,000)	
	316 (4,000)		314 (+15,000)	276 (+2,400)	
	282 (2,100)[e]				
	255 (12,000)		254 (+38,000)		233
		228 (−2,700)			
	214 (27,000)				
(α*S*)-**6c**		500 (±0)			460
	417 (1,200)		417 (+1,400)	370 (+600)	
	328 (3,500)		328 (+12,000)	282 (±0)	
	277 (2,400)[e]				
	255 (10,000)[e,g]		256 (+24,000)		243
		240 (−12,000)			
(α*S*)-**7c**		500 (±0)			470
	417 (1,200)		417 (+3,000)	378 (+1,200)	
	327 (3,500)		328 (+7,800)	275 (+2,000)	
	280 (2,400)[e]				
	253 (12,000)[e]		256 (+20,000)	243 (+10,000)	
	223 (38,000)		233 (+21,000)		226
		220 (−15,000)			
(α*R*)-**13c**		500 (±0)			455
	415 (1,300)		417 (−1,300)	370 (−500)	
	327 (3,400)		327 (−10,000)	282 (−300)	
	276 (2,500)[e]				
	252 (10,000)[e]		256 (−21,000)		243
		230 (+38,000)			
	222 (31,000)				
(α*S*)-**14c**		500 (±0)			460
	415 (1,400)		412 (+2,700)	367 (+1,000)	
	327 (3,500)		327 (+5,000)		293
	277 (2,400)		275 (−1,600)		268
	253 (11,000)[e,g]		255 (+16,000)	239 (+6,800)	
		235 (+10,000)			
(α*S*)-**14d**		500 (±0)			450
	402 (1,100)		400 (+2,400)	360 (+700)	
	316 (3,900)		315 (+6,200)		280
	278 (3,300)[e]		272 (−1,800)		268
	255 (14,000)[f]		253 (+16,000)	235 (+3,000)	
		225 (+13,000)			

[a] *c* 0.00177–0.0280 g/100 ml; length 1 cm; temperature 25–28°. [b] Molecular ellipticity. [c] Molecular absorptivity. [d] Each first entry at a longer wavelength than a maximum indicates the interval from the longest wavelength examined for which [θ] = ±0. [e] Shoulder. [f] Spectrum below 225 nm not determined. [g] Spectrum below 240 nm not determined.

phethamine dihydrochloride [(*S*)-**5a**] induces an increase rather than a decrease in 5-HT, while (*R*)-**5a** had no effect. Tryptophan hydroxylase activity is not appreciably changed with either (*S*)-**5a** or (*R*)-**5a**.

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Optical rotations at the sodium D line were measured using a visual polarimeter and 1-dm sample tubes. Pmr spectra were determined with a Varian A-60 or JEOL MH-100 spectrometer and chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS as internal standard. All compounds gave pmr signals compatible with their assigned structures and relative configurations, but only those signals necessary for differentiating the various compounds are given. Isotropic electronic absorption (EA) spectra were measured with a Cary Model 14 spectrophotometer with the normal variable slit and circular dichroism (CD) spectra with a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory and programmed for a spectral band width of 1.5 nm. Elemental analyses where indicated were done by Galbraith Laboratories, Inc., Knoxville, Tenn., and, unless noted otherwise, were within ±0.30% of the calculated values.

(*S*)-(+)-*p*-**Chloroamphetamine Hydrochloride** [(*S*)-**1a**]. To a solution of $NaNO_2$ (152 mg, 2.20 mmol) in concentrated H_2SO_4 (1.6 ml), stirred at 0°, was added glacial HOAc (5 ml) followed by (*S*)-**19** (632 mg, 2.00 mmol) in portions. The mixture was stirred 30 min at 0° and then was added slowly to a freshly prepared solution of CuCl (5.0 mmol), prepared from $CuSO_4 \cdot 5H_2O$ (5.0 mmol) and NaCl (5.6 mmol) by the bisulfite procedure,[28] in concentrated HCl (4 ml) at 0°. The mixture was allowed to warm to room temperature and, after stirring overnight, was heated 20 min on the steam bath. It was cooled, diluted with H_2O (20 ml),

Table III. Effects of Various β-Phenylethylamine Hydrochlorides on the Level of 5-Hydroxytryptamine (5-HT) and the Activity of Tryptophan Hydroxylase (TH) in Rat Brain[a]

Compd	Dose, mg/kg[b]	% control ± S.E.M.[c] 4 hr after injection		% control ± S.E.M.[c] 2 weeks after injection	
		5-HT	TH	5-HT	TH
(S)-1a	5	63.9 ± 3.6[d]	55.1 ± 3.4[d]	46.6 ± 4.1[d]	64.1 ± 4.1[d]
(R)-1a	5	34.9 ± 1.6[d]	62.7 ± 2.0[d]	61.6 ± 1.6[d]	92.3 ± 4.5[e]
(S)-4a	15	41.5 ± 0.9[d]	54.6 ± 1.9[d]	81.3 ± 9.5[f]	71.8 ± 6.4[g]
(R)-4a	15	16.4 ± 1.2[d]	51.7 ± 3.0[d]	68.1 ± 7.8[f]	76.5 ± 2.1[g]
(S)-5a	15	170.6 ± 9.5[d]	87.0 ± 0.9[e]		
(R)-5a	15	100.9 ± 5.6[e]	89.4 ± 4.0[e]		
(αS)-**6a**	10	92.8 ± 3.8[e]	88.1 ± 6.3[e]	89.5 ± 4.1[e]	79.9 ± 5.1[f]
(αR)-**6a**	10	110.7 ± 2.1[e]	96.7 ± 7.1[e]	100.1 ± 3.7[e]	110.7 ± 3.3[e]
(αS)-**7a**	10	106.1 ± 3.7[e]	106.2 ± 3.7[e]	94.6 ± 2.5[e]	93.4 ± 4.2[e]
(αR)-**7a**	10	91.8 ± 5.5[e]	86.2 ± 3.6[e]	93.6 ± 2.6[e]	97.2 ± 7.0[e]

[a]Groups of five or six rats were injected intraperitoneally. The animals were killed 4 hr or 2 weeks later and the levels of 5-HT and TH activity in whole brain were determined. [b]Expressed as weight of the free base. [c]Results are mean values of five or six rats; S.E.M. is the standard error of the mean. Each value in the experimental group was calculated as the per cent of the mean value for a group of control rats, analyzed the same day. Mean values for all control animals were 5-HT, 0.34 ± 0.02 μg/g ($n = 22$), and TH, 34.5 ± 1.5 nCi of [^{14}C]-5-HT formed per gram per hour ($n = 28$). The probable significance level (p) between each test group and the appropriate control group was determined by Student's t test and is given as a footnote. [d]$p < 0.001$. [e]$p > 0.05$. [f]$p < 0.05$. [g]$p < 0.01$.

Table IV. Properties of Optically Pure N-5-Bromosalicylidene and N-Salicylidene Derivatives

Compd[a]	Recrystn solvent	Mp, °C	$[\alpha]^{24-25}$D, deg[b]	Analyses
(R)-**1c**	*i*-PrOH	116–117	−209	C, H, N
(S)-**2c**	95% EtOH	86–87	+234	*c*
(S)-**2d**	95% EtOH	56–57	+348	*d*
(αS)-**6c**	*i*-PrOH–hexane	100–101	+70	C, H, N
(αS)-**7c**[e]	CCl_4	109–110	+140	C, H
(αR)-**13c**	*i*-PrOH–hexane	99–100	−118	C, H, Br, N
(αS)-**14c**	Cyclohexane	100–102	+179	C, H
(αS)-**14d**	Cyclohexane	97–98	+226	C, H, N

[a]Yellow or orange crystalline solid. [b]In absolute EtOH, c 0.74–1.34 g/100 ml. [c]Lit.[23] mp 87–88°; $[\alpha]^{25}$D +186° (c 0.9, absolute EtOH). [d]Lit.[23] mp 58–60°; $[\alpha]^{24}$D +346° (c 1.0, absolute EtOH). [e]$C_{16}H_{15}BrClNO_2 \cdot {}^1/_3CCl_4$.

and extracted with Et_2O. The ether extract was washed with H_2O, 5% NaOH, and again with H_2O, dried ($MgSO_4$), and evaporated to an oily residue (600 mg) which was dissolved in 95% EtOH (3.5 ml) and boiled for 5 hr with 85% NH_2NH_2 in H_2O (144 mg). The mixture was cooled and filtered to remove phthaloylhydrazine, and the filtrate was acidified with 6 N HCl and evaporated to near dryness. The residue was dissolved in H_2O (0.5 ml). This solution was filtered and the filtrate evaporated to dryness yielding (S)-1a (310 mg, 75%) which was recrystallized from Me_2CO–MeOH: mp 196–198°; $[\alpha]^{25}$D +22° (c 1.90, H_2O) [lit.[6] mp 199–199.5°; $[\alpha]^{20}$D +19.2° (c 5, H_2O)]. *Anal.* ($C_9H_{13}Cl_2N$) C, H, Cl, N.

(R)-(−)-*p*-**Chloroamphetamine Hydrochloride** [(R)-1a]. (R)-*p*-Chloroamphetamine L-N-acetylleucinate was prepared as outlined previously[6] and after three recrystallizations from water had $[\alpha]^{25}$D −29° (c 0.96, H_2O). Decomposition of the salt in the usual way gave (R)-**1a**: mp 198–199°; $[\alpha]^{25}$D −22° (c 1.90, H_2O). (S)-*p*-Chloroamphetamine D-N-acetylleucinate, obtained from the partially resolved amine hydrochloride from the mother liquors of the resolution outlined above, had $[\alpha]^{25}$D +28° (c 0.97, H_2O). Decomposition of this salt gave (S)-**1a**: mp 198–199°; $[\alpha]^{25}$D +21° (c 2.02, H_2O).

(S)-(+)- and (R)-(−)-*p*-**nitroamphetamine hydrochloride** [(S)- and (R)-4a], prepared as described previously,[8] had mp 194–195° and 193–194°; $[\alpha]^{25}$D +21° (c 1.22, H_2O) and −17° (c 1.24, H_2O), respectively [lit.[8] mp 197–199°; $[\alpha]^{20}$D +22.0° (c 1.218, H_2O) for the S isomer].

(S)-(+)- and (R)-(−)-*p*-**aminoamphetamine dihydrochloride** [(S)- and (R)-5a], obtained by hydrogenation of (S)- and (R)-4a, respectively, over Pt in absolute EtOH had, after recrystallization from EtOH–Et_2O, mp 270° dec and 265° dec; $[\alpha]^{25}$D +16° (c 1.23, H_2O) and −19° (c 1.22, H_2O), respectively [lit.[9] $[\alpha]^{24}$D +16.5° (c 1.0, H_2O) for the S isomer].

(±)-*p*-**Chloronorephedrine Hydrochloride** [(±)-6a]. Nitrosation of 4′-chloropropiophenone[15] followed by hydrogenation in MeOH–HCl over 10% Pd/C at 30 psi until 2 equiv of H_2 had reacted gave, after recrystallization from EtOH–Et_2O, 2-amino-4′-chloropropiophenone hydrochloride (42% overall): mp 218–222° dec (lit.[16] mp 220–222° dec). Treatment of this ketone (11.0 g, 50.0 mmol) with $NaBH_4$ (2.0 g, 53 mmol) in MeOH (100 ml) gave, after recrystallization from EtOH–Et_2O, (±)-6a (8.55 g, 77%), mp 244–246° dec (lit. mp 244–245°[15] and 245–246°[16]).

(αR)-(+)- and (αS)-(−)-*p*-**Chloronorephedrine Hydrochloride** [(αS)- and (αR)-6a]. A solution of N-acetyl-L-leucine (4.33 g, 25.0 mmol) and NaOH (1.00 g, 25.0 mmol) in H_2O (50 ml) was added to a solution of (±)-6a (11.1 g, 50.0 mmol) in H_2O (100 ml). The resulting precipitate was collected and recrystallized three times from water to give the optically pure salt (1.5 g, 17%): mp 224–225° dec; $[\alpha]^{25}$D +4° (c 1.02, H_2O). The salt was mixed with aqueous NaOH, the amine extracted into Et_2O, and the Et_2O solution extracted with 2 N HCl. This aqueous solution was evaporated to dryness. Recrystallization of the residue from 95% EtOH gave (αR)-6a (0.56 g, 60%): mp 224–232° dec; $[\alpha]^{25}$D +35° (c 1.92, H_2O). *Anal.* ($C_9H_{13}Cl_2NO$) Cl.

Partially racemic (αS)-6a, $[\alpha]^{25}$D −12° (c 2.66, H_2O) (4.00 g, 18.0 mmol) was dissolved in H_2O (75 ml), and to it was added a solution of N-acetyl-D-leucine (3.12 g, 18.0 mmol) and NaOH (0.75 g, 19 mmol) in H_2O (25 ml). Two recrystallizations of the resulting precipitate from H_2O gave the optically pure salt (1.45 g). Decomposition of this salt as outlined for (αR)-6a and recrystallization from 95% EtOH gave (αS)-6a (0.63 g, 70%): mp 223–235° dec; $[\alpha]^{25}$D −35° (c 3.07, H_2O).

(±)-*p*-**Chloronorpseudoephedrine Hydrochloride** [(±)-7a]. (±)-N-Acetyl-*p*-chloronorephedrine, mp 202–204° (lit.[16] mp 207°) (10.5 g, 46.1 mmol), prepared from (±-6a, was added in small portions to excess $SOCl_2$ (25 ml), stirred and ice-cooled. Stirring was continued for 45 min; then 20% aqueous NaOH (45 ml) was added, the mixture was extracted with three portions of Et_2O, and the Et_2O solution was extracted with 2 N HCl. Evaporation of the acid solution and recrystallization of the residue from EtOH–Et_2O gave (±)-7a (6.30 g, 62%): mp 236–238° dec (lit.[16] mp 238–238.5°).

(αS)-(+)- and (αR)-(−)-*p*-**chloronorpseudoephedrine hydrochloride** [(αS)- and (αR)-7a] had mp 277–278° dec and 275–276° dec; $[\alpha]^{25}$D +39° (c 2.00, H_2O) and −39° (c 2.02, H_2O), respectively.

(αR)-(+)-**Norephedrine hydrochloride** [(αR)-13a], prepared by resolution of (±)-13a with tartaric acid,[17] had mp 169–171°; $[\alpha]^{25}$D +32° (c 1.07, H_2O) [lit.[17] mp 171–172°; $[\alpha]^{27}$D +33.40° (c 6.5265, H_2O)].

(αS)-(+)-**Norpseudoephedrine hydrochloride** [(αS)-**14a**], mp 180–182°, $[\alpha]^{25}D$ +43° (*c* 6.16, H_2O) [lit.[17] mp 180–181°, $[\alpha]^{20}D$ +42.53° (*c* 7.1017, H_2O)], was purchased from K and K Laboratories, Inc.

(*S*)-(+)-*N*-(**2-Carboxybenzoyl**)-*p*-**nitroamphetamine** [(*S*)-**17**]. A solution of (*S*)-*p*-nitroamphetamine [(*S*)-**4b**] (11.6 g, 64.4 mmol), obtained from (*S*)-**4a**, in dry ether (50 ml) was added dropwise to a stirred suspension of phthalic anhydride (9.54 g, 64.4 mmol) in dry ether (300 ml), and stirring was continued for 20 hr. The resulting precipitate was collected and recrystallized from water to give (*S*)-**17** (12.3 g, 58%): mp 153–154°; $[\alpha]^{25}D$ +52° (*c* 2.10, absolute EtOH); pmr (C_5D_5N) 14.9 ppm (br s, 1, CO_2H). *Anal.* ($C_{17}H_{16}N_2O_5$) C, H; N: calcd, 8.53; found, 9.18.

(*S*)-(+)-*N*-**Phthaloyl**-*p*-**nitroamphetamine** [(*S*)-**18**]. A mixture of (*S*)-**17** (3.9 g, 12 mmol) and 4% ethanolic HCl (125 ml) was boiled for 4 hr and then evaporated to dryness. The residue was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ layer was washed with saturated $NaHCO_3$ solution and with H_2O, dried (Na_2SO_4), and evaporated to dryness. Recrystallization of the residue from absolute EtOH gave (*S*)-**18** (2.3 g, 62%): mp 135–136°; $[\alpha]^{25}D$ +199° (*c* 1.50, $CHCl_3$). *Anal.* ($C_{17}H_{14}N_2O_4$) C, H, N.

(*S*)-(+)-*N*-**Phthaloyl**-*p*-**aminoamphetamine Hydrochloride** [(*S*)-**19**]. A solution of (*S*)-**18** (2.0 g, 64 mmol) in absolute EtOH (300 ml) was hydrogenated 3 hr over Pt (from 28 mg of PtO_2) at 54 psi. The mixture was filtered, and the filtrate was concentrated, diluted with benzene, and saturated with dry HCl. The solvents were evaporated and recrystallization of the residue from absolute EtOH–Et_2O gave (*S*)-**19** (1.2 g, 59%): mp 230° dec; $[\alpha]^{25}D$ +173° (*c* 1.22, absolute EtOH). *Anal.* ($C_{17}H_{17}ClN_2O_2$) C, H, Cl, N.

N-**5-Bromosalicylidene and** *N*-**Salicylidene Derivatives.** Each amine hydrochloride was decomposed with NaOH solution and the residue was extracted with Et_2O. The amine obtained after evaporation of the dried ($MgSO_4$) extract was dissolved in nine times its weight of MeOH. An equimolar amount of 5-bromosalicylaldehyde or a 10% molar excess of salicylaldehyde was added. The resulting precipitate was collected and recrystallized from an appropriate solvent, except for the norephedrine derivatives which are soluble in MeOH. In these cases the MeOH was evaporated and the residue was recrystallized as indicated. Results are summarized in Table IV.

Determination of Brain 5-Hydroxytryptamine (5-HT) and Tryptophan Hydroxylase Activity. Male rats obtained from the Sprague-Dawley Co. (Madison, Wis.) were used. All drugs were injected intraperitoneally and the doses are expressed in terms of the free base. The rats were kept under standard housing conditions (16 × 10 × 7 in. stainless steel cages, four to five animals per cage, environmental temperature 21–24°, constant light-dark cycle with 6 p.m. to 5 a.m. dark) and had free access to Purina rat chow and water. Four hours or 2 weeks after the administration of the drugs, groups of rats were killed by decapitation and 5-HT levels and tryptophan hydroxylase activity were assayed in whole brains. The brains were rapidly removed, frozen on Dry Ice, and stored at 5° until analyzed. For analysis, whole brains were homogenized in 3 vol of ice-cold 0.05 *M* Tris acetate buffer, and a 0.3-ml aliquot of the homogenate was removed and assayed for tryptophan hydroxylase activity by modification[3] of a method described previously.[29] The remaining sample was homogenized again after the addition of 0.2 ml of 2 *N* HCl. The amount of 5-HT in this sample was determined by a spectrophotofluorometric method.[30]

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