Phenylalkylamines with Potential Psychotherapeutic Utility. 2. Nuclear Substituted 2-Amino-1-phenylbutanes

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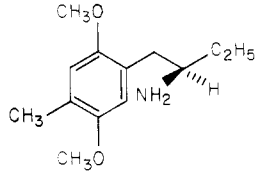
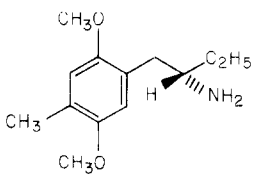
A series of 2-amino-1-(4-substituted-2,5-dimethoxyphenyl)butanes (Table V) was prepared as analogues of (*R*)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane (**1a**). 1-(2,5-Dimethoxyphenyl)-2-(*N*-phthalimido)butane (**7**) was utilized as a synthetic intermediate common to many of the target compounds. Animal data are presented indicating that most of these analogues have low hallucinogenic potential. Selected compounds were compared with **1a** in an avoidance-response acquisition model which differentiates between **1a** and the human hallucinogens DOM (**2a**) and DOET (**2b**). Structure–activity relationships of these analogues are discussed.

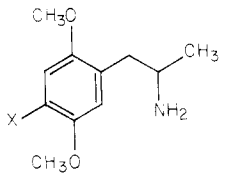
In the course of a program directed at potential nonhallucinogenic performance-enhancing agents, we had prepared (*R*)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane (**1a**, dimoxamine,[1] BL-3912A).[2] This



1a (*R* isomer)



1b (*S* isomer)



2a (DOM), X = CH_3
b (DOET), X = C_2H_5
c (DOB), X = Br

compound, a homologue of the well-known hallucinogen DOM (**2a**),[3] presented an activity profile in animals strikingly different from that of **2a**. In addition to exhibiting low hallucinogenic potential in the rabbit hyperthermia test, **1a** enhanced avoidance acquisition in the rat[2] and has been shown to block the serotonergic action of **2a** in vitro.[4]

In the hallucinogenic phenylisopropylamines, particularly potent compounds are obtained when a nuclear 2,5-dimethoxy substitution is combined with an appropriate 4 substitutent;[5,6] DOM, DOET, and DOB (**2a**, **2b**, and **2c**, respectively) are notable examples.[3,7] Furthermore, qualitative as well as quantitative differences in human activity with 4-substituent variation have been reported.[3,5,7,8]

Therefore, as a first approach to investigating structure–activity relationships in our phenyl-*sec*-butylamine series, we elected to retain the 2,5-dimethoxy substitution pattern and to investigate the effect of replacing the nuclear 4-methyl moiety in **1**. This would provide a series of compounds parallel to the psychotomimetic phenylisopropylamines represented by structure **2** from which interesting comparisons between the effect of a given substituent upon hallucinogenic activity and performance-enhancing properties could be derived.

Chemistry. Emphasis throughout this work was placed upon obtaining *R* isomers, since **1a** is the more active isomer in avoidance acquisition.[2] The desired optically active compounds could be readily prepared from the requisite aldehydes via the stereoselective synthesis described previously.[2,9] In the phenylisopropylamine series **2**, it has been shown[9] that the absolute configuration of the product amine was the same as that of the α-methylbenzylamine isomer employed. Configurational assignments in the case of **2a** isomers were made by Castagnoli et al. on the basis of CD curves.[10] It was also noted[9,10] that diastereomeric amides of the *R* and *S* isomers were eluted on GLC in a predictable order. For instance, in the case of amides derived from (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(−)-MTPA], amides of *R* isomers were eluted before amides of the corresponding *S* isomers.

It has previously been shown by us[2] that these relationships also applied to **1** isomers. Further, the configuration of **1a** was confirmed by comparison of its ORD curve with that of (*S*)-amphetamine. Unequivocal synthesis of phenyl-*sec*-butylamines of desired configuration could thus confidently be undertaken.

Alternatively, $LiAlH_4$ reduction of the intermediate nitroolefins **3** provided racemic amines **6**. In one case (**6d**, Table V), resolution was accomplished utilizing (+)- and (−)-2′-nitrotartranilic acids.[11]

The compounds actually prepared by these methods and the appropriate intermediates are listed in Tables I–III and V.

Preparation of 1-[2,5-dimethoxy-4-(2-propyl)phenyl]-2-nitro-1-butene (**3c**) required a somewhat modified procedure which is detailed in the Experimental Section. After

(1) USAN for (*R*)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride; *J. Am. Med. Assoc.*, **238**, 1407 (1977).
(2) For paper 1 in this series, see R. T. Standridge, H. G. Howell, J. A. Gylys, R. A. Partyka, and A. T. Shulgin, *J. Med. Chem.*, **19**, 1400 (1976).
(3) A. T. Shulgin and D. C. Dyer, *J. Med. Chem.*, 18, 1201 (1975), and references cited therein.
(4) Donald C. Dyer, *Res. Commun. Chem. Pathol. Pharmacol.*, 14, 449 (1976).
(5) A. T. Shulgin in "Psychotomimetic Drugs", D. H. Efron, Ed., Raven Press, New York, 1970, pp 34–35.
(6) F. A. B. Aldous, B. C. Barrass, K. Brewster, D. A. Buxton, D. M. Green, R. M. Pinder, P. Rich, M. Skeels, and K. J. Tutt, *J. Med. Chem.*, 17, 1100 (1974).
(7) A. T. Shulgin, T. Sargent, and C. Naranjo, *Pharmacology*, 5, 103 (1971).
(8) S. H. Snyder, H. Weingartner, and L. A. Faillace, *Arch. Gen. Psychiatry*, **24**, 50 (1971).
(9) D. E. Nichols, C. F. Barfknecht, D. B. Rusterholz, F. Benington, and R. D. Morin, *J. Med. Chem.*, **16**, 480 (1973).
(10) S. B. Matin, P. S. Callery, J. S. Zweig, A. O'Brien R. Rapoport, and N. Castagnoli, Jr., *J. Med. Chem.*, 17, 877 (1974).
(11) T. A. Montzka, T. L. Pindell, and J. D. Matiskella, *J. Org. Chem.*, 33, 3993 (1968).

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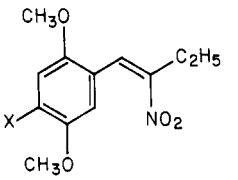
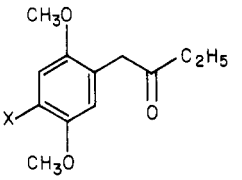
Table I. 1-(4-Substituted-2,5-dimethoxyphenyl)-2-nitro-1-butenes 3a–d



no.	X	mp, °C	% yield	recrystn solv	formula	anal.
3a[a]	H	44–46	32	MeOH-H_2O	$C_{12}H_{15}NO_4$	C, H, N
3b[a]	Et	64.5–66.5	42	MeOH	$C_{14}H_{19}NO_4$	C, H, N
3c	*i*-Pr	60.5–62.5	48	pentane	$C_{15}H_{21}NO_4$	C, H, N
3d[b]	CH_3S	103–105	70	EtOH-H_2O	$C_{13}H_{14}NO_4S$	C, H, N

[a] Prepared by the procedure detailed in ref 2. [b] Prepared by the "improved" procedure for 3 (X = CH_3). See Experimental Section.

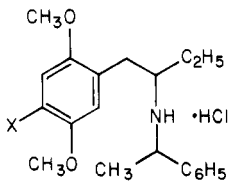
Table II. 1-(4-Substituted-2,5-dimethoxyphenyl)-2-butanones 4a–c



no.[a]	X	mp or bp (mm), °C	% yield	recrystn solv	formula	anal.
4a	H	121–124 (0.6)	62	Skelly B	$C_{12}H_{16}O_3$	C, H
4b	Et	37–39	83		$C_{14}H_{20}O_3$	C, H
4c	*i*-Pr	117–120 (0.05)	79		$C_{15}H_{22}O_3$	C, H

[a] Compounds were prepared by the procedure detailed in ref 2.

Table III. 1-(4-Substituted-2,5-dimethoxyphenyl)-2-(α-methylbenzylamino)butanes 5a–c



no.[a]	X	mp, °C	% yield	recrystn solv	opt isomer	$[\alpha]^t_{365}$,[b] deg	formula	anal.
5a	H	228.5–230	50	MeCN	*R,R*	+51.3 (25)	$C_{20}H_{27}NO_2 \cdot HCl$	C, H, N
5a	H	227.5–229.5	45	MeCN	*S,S*	−50.5 (23.5)	$C_{20}H_{27}NO_2 \cdot HCl$	C, H, N
5b	Et	216–218.5	67	$MeNO_2$	*R,R*	+88.4 (24)	$C_{22}H_{31}NO_2 \cdot HCl$	C, H, N
5b	Et	215.5–218.5	72	$MeNO_2$	*S,S*	−81.3 (23)	$C_{22}H_{31}NO_2 \cdot HCl$	C, H, N
5c	*i*-Pr	230–233	44	Et_2O	*R,R*	+96.5 (20)	$C_{23}H_{33}NO_2 \cdot HCl$	C, H, N

[a] Compounds were prepared by the procedure detailed in ref 2. [b] *c* 1.0, 95% EtOH.

this work was completed, a more attractive method of preparation of nitroolefins of this type was noted.[12] Suitable modifications gave excellent results with 1-(2,5-dimethoxy-4-methylphenyl)-2-nitro-1-butene (**3**, X = CH_3).

The stereoselective sequence,[2] though effective and optically efficient, became tedious when applied to a lengthy series of compounds. An attractive alternative was the use of 2-amino-1-(2,5-dimethoxyphenyl)butane (**6a**), suitably protected, as a common intermediate. This procedure considerably shortened the individual sequences and offered an additional advantage in that by starting with **6a** of known configuration, product amines of the same configuration could be prepared without the necessity of separate asymmetric synthesis or resolution. This approach is outlined in Scheme I.

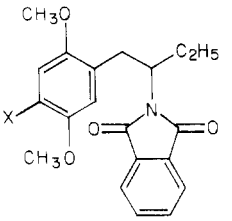
A number of DOM relatives had been prepared by Coutts and Malicky through an *N*-acetyl precursor.[13] However, removal of the protecting group required stringent basic conditions. Ho[14] had employed an *N*-phthaloyl protecting group in the synthesis of some DOM metabolites; Sargent and co-workers[21] have recently reported application of this method to the preparation of a series of radiolabeled 4-iodo-2,5-dimethoxyphenylalkylamines. This protecting group was also found by us to be quite satisfactory. Following appropriate synthetic manipula-

(12) J. S. Zweig and N. Castagnoli, Jr., *J. Med. Chem.*, **20**, 414 (1977).

(13) R. T. Coutts and J. M. Malicky, *Can. J. Chem.*, **51**, 1402 (1973).

(14) B. T. Ho and L. W. Tansey, *J. Med. Chem.*, **14**, 156 (1971).

Table IV. 1-(4-Substituted-2,5-dimethoxyphenyl)-2-(*N*-phthalimido)butanes



no.	X	mp, °C	% yield	recrystn solv	opt isomer	$[\alpha]^t_D$,[a] deg	procedure	formula	anal.
7[d]	H	77–80	95		(±)		A	$C_{20}H_{21}NO_4$	C, H, N
7	H	oil	100		*R*	−183.2 (25)	A	$C_{20}H_{21}NO_4$	C, H, N
8a	MeCO	107–109.5	75	Skelly B	(±)		B	$C_{22}H_{23}NO_5$	C, H, N
8b	EtCO	94–97	51	Skelly B	(±)		B	$C_{23}H_{25}NO_5$	C, H, N
8b	EtCO	112–113	61	EtOH	*R*	−218.3 (25)	B	$C_{23}H_{25}NO_5$	C, H, N
8c	*n*-PrCO		68	EtOH-H_2O	*R*		B	$C_{24}H_{27}NO_5$	*c*
10	CHO	92–96	43	EtOH	(±)		D	$C_{21}H_{21}NO_5$	C, H, N
10	CHO	111–113	64	MeOH-H_2O	*R*	−258.6 (25)	D	$C_{21}H_{21}NO_5$	C, H, N
11	OH	120.5–123	82	EtOH-H_2O	(±)		E	$C_{20}H_{21}NO_5$	C, H, N
11	OH	123–125	70	*i*-PrOH	*R*	−176.2 (23)	E	$C_{20}H_{21}NO_5$	C, H, N
14	NO_2	140.5–142.5	90	EtOH	*R*	−224.8[b] (23)		$C_{20}H_{20}N_2O_6$	C, H, N
15	NH_2	141–142.5	90	EtOH-H_2O	*R*	−197.6[b] (24)		$C_{20}H_{22}N_2O_4$	C, H, N

[a] *c* 1.0, 95% EtOH. [b] *c* 1.0, $CHCl_3$. [c] >99% pure by GC. Used directly in the preparation of **9b** (Table V). [d] Not analyzed; see ref 21.

Scheme I

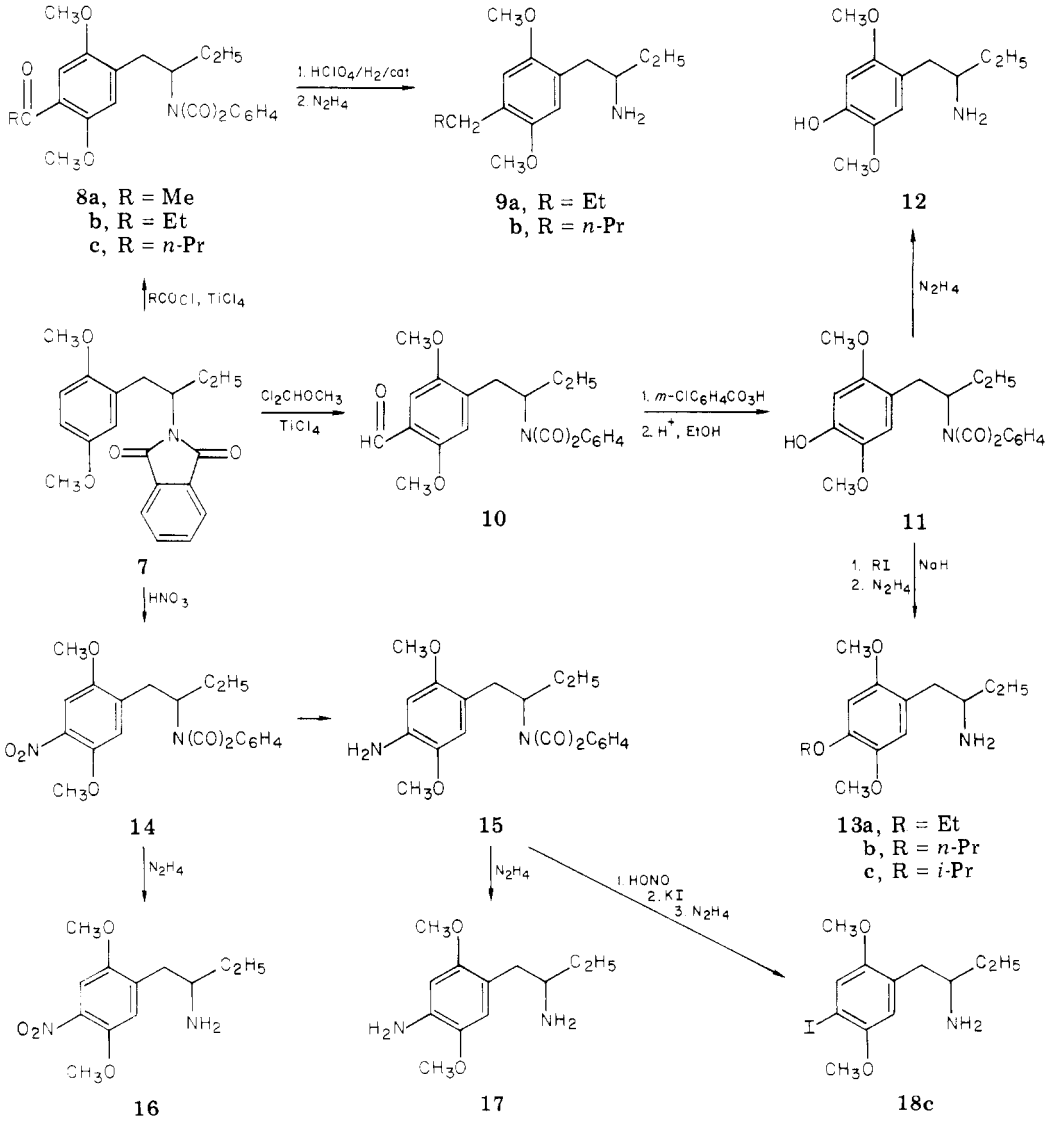
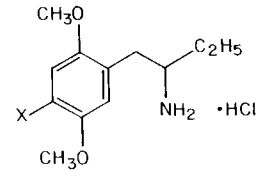


Table V. Some Synthetic and Pharmacological Data of 1-Amino-2-(4-substituted-2,5-dimethoxyphenyl)butanes



no.	X	mp, °C	% yield	recrystn solv	opt isomer	$[\alpha]^t_{365}$,[b] deg	procedure	formula	anal.	cat behavior N[h]	cat behavior cat score[i]
6a	H	175–177	56	MeCN	(±)		*a*	$C_{12}H_{19}NO_2$·HCl	C, H, N, Cl	2	2 (2, 2)
6a	H	140–142	83	MeCN	*R*	−44.2 (23)	*a*	$C_{12}H_{19}NO_2$·HCl	C, H, N, Cl	2	0.5 (1, 0)
6a	H	141–144	42	*i*-PrOH–Et_2O	*S*	+44.3 (20)	*a*	$C_{12}H_{19}NO_2$·HCl	C, H, N, Cl	2	2 (2, 2)
1a	Me				*R*		*a*			4	1.3 ± 0.5
1b	Me				*S*		*a*			4	0.5 ± 0.3
6b	Et	223.5–225	54	MeOH–Et_2O	(±)		*a*	$C_{14}H_{23}NO_2$·HCl	C, H, N, Cl	4	4.0 ± 0.6
6b	Et	236.5–238	81	*i*-PrOH	*R*	−50.2 (24)	*a*	$C_{14}H_{23}NO_2$·HCl	C, H, N, Cl	4	3.3 ± 0.7
6b	Et	236.5–238	75	*i*-PrOH	*S*	+51.1 (25)	*a*	$C_{14}H_{23}NO_2$·HCl	C, H, N, Cl	2	1 (1, 1)
6c	*i*-Pr	217–219	60	MeCN	(±)		*a*	$C_{15}H_{25}NO_2$·HCl	C, H, N, Cl	2	0.5 (1, 0)
6c	*i*-Pr	210–212	89	MeCN	*R*	−50.8 (24)	*a*	$C_{15}H_{25}NO_2$·HCl	C, H, N	2	0 (0, 0)
6d	MeS	220–221	65	EtOH–Et_2O	(±)		*a*	$C_{13}H_{21}NO_2S$·HCl	C, H, N	2	1 (0, 2)
6d	MeS	254–256	11	EtOH	*R*	−79.5 (24)		$C_{13}H_{21}NO_2S$·HCl	C, H, N, Cl	4	1.3 ± 0.8
6d	MeS	254–256	29	EtOH	*S*	+79.9 (24)		$C_{13}H_{21}NO_2S$·HCl	C, H, N, Cl	2	1 (1, 1)
9a	*n*-Pr	230–233.5	42	MeCN	(±)		C	$C_{15}H_{25}NO_2$·HCl	C, H, N	2	2.5 (3, 2)
9a	*n*-Pr	174.5–176.5	82	MeCN	*R*	−10.9 (23.5)[d]	C	$C_{15}H_{25}NO_2$·HCl	C, H, N	2	0.5 (0, 1)
9b	*n*-Bu	156–158	75	MeCN	*R*	−43.9 (21)	C	$C_{16}H_{27}NO_2$·HCl	C, H, N, Cl	2	0 (0, 0)
12	OH[c]	150–150.5	24	EtOAc	*R*	−39.5 (21.5)[d]	G	$C_{12}H_{19}NO_3$	C, H, N	2	0.5 (0, 1)
13a	EtO	189–190.5	50	Me_2CO	*R*	−13.9 (23)[d]	F	$C_{14}H_{23}NO_3$·HCl	C, H, N, Cl	2	1.5 (1, 2)
13b	*n*-PrO	194.5–196	12	*i*-PrOH	(±)		F	$C_{15}H_{25}NO_3$·HCl	C, H, N, Cl	2	0 (0, 0)[j]
13b	*n*-PrO	167–168.5	69	*i*-PrOH–Et_2O	*R*	−13.3 (24)[d]	F	$C_{15}H_{25}NO_3$·HCl	C, H, N, Cl	2	1.5 (1, 2)
13c	*i*-PrO	156.5–158.5	65	*i*-PrOH–Et_2O, Me_2CO	*R*	−12.1 (23.5)[d]	F	$C_{15}H_{25}NO_3$·HCl	C, H, N, Cl	2	0 (0, 0)
16	NO_2	223–224[f]	69	*i*-PrOH	*R*	−25.0 (24)[d,e]	G	$C_{12}H_{18}N_2O_4$·HCl	C, H, N, Cl	2	3.5 (3, 4)
17	NH_2[c]	79–80	65	H_2O	*R*	−210.1 (23.5)	G	$C_{12}H_{20}N_2O_2$	C, H, N	2	1.5 (1, 2)
18a	Cl	215–216.5	53	$MeNO_2$	*R*	−60.8 (24)	H[g]	$C_{12}H_{18}ClNO_2$·HCl	C, H, N, Cl	2	6.5 (6, 7)
18b	Br	206–209	69	EtOH–Et_2O	(±)		H	$C_{12}H_{18}BrNO_2$·HCl	C, H, N, X[l]	2	2 (2, 2)
18b	Br	240–242	71	*i*-PrOH	*R*	−57.0 (24)	H	$C_{12}H_{18}BrNO_2$·HCl	C, H, N, X[l]	4	3.5 ± 0.9
18b	Br	241–243	53	*i*-PrOH	*S*	+57.6 (24)	H	$C_{12}H_{18}BrNO_2$·HCl	C, H, N, X[l]	2	2 (2, 2)
18c[k]	I	255.5–257	44	*i*-PrOH	*R*	−56.8 (24)		$C_{12}H_{18}INO_2$·HCl	C,[m] H, N, I	2	2.5 (2, 3)

[a] Prepared by procedures detailed in ref 2. [b] *c* 1.0, 95% EtOH. [c] Free base. [d] λ 589 nm. [e] *c* 1.0, H_2O. [f] Greenish-yellow needles. [g] 1.25 mol of Cl_2/mol of (*R*)-6a utilized. [h] Number of animals. [i] Numerical score on cat behavior observation at a dose of 10 mg/kg sc. For $N = 2$, scores are averages with the individual values in parentheses. For $N = 4$, scores are means plus or minus standard error. Scores for reference agents (dose, mg/kg sc): (*R*)-DOM, 12 (0.5); (*R*)-DOET, 10.5 (0.1); (*R*)-DOB, 17.5 (1). Reference *R* isomers proved to be consistently more active (10–100×) than the corresponding *S* isomers. [j] Dose = 5 mg/kg sc. [k] The racemic form (radiolabeled) of this compound has been reported; see ref 21. [l] X = halogen. [m] C: calcd, 38.78; found, 39.27.

tions, hydrazinolysis to the final products was accomplished under mild conditions. Optical purity checks utilizing (−)-MTPA amides[2] confirmed that no racemization occurred during the preparative sequences.

Thus, 1-(2,5-dimethoxyphenyl)-2-(*N*-phthaloyl)butane (**7**) reacted smoothly with acid chlorides to give the 4-acyl derivatives **8**. Use of $TiCl_4$ as catalyst gave none of the partial O-demethylation noted by Shulgin and Dyer[3] with $AlCl_3$ in related acylations. Catalytic reduction, followed by hydrazinolysis, yielded the desired 4-alkyl compounds **9**.

Similarly, **7** could be formylated with dichloromethyl methyl ether, giving the aldehyde **10**. Standard Vilsmeier formylation, as employed by Ho[14] upon 1-(2,5-dimethoxyphenyl)-2-(*N*-phthaloyl)propane, was not successful. The aldehyde **10** underwent the Baeyer–Villiger rearrangement, yielding the phenol **11**. This afforded the alkoxy derivatives **13**, as well as the parent aminophenol **12**. The aldehyde **10** can also be employed in the synthesis of the corresponding hydroxymethyl and carboxylic acid derivatives, which are potential metabolites of **1**.[14] This will be reported in a future publication.

Nitration of **7** provided **14**, which was catalytically reduced to **15**. These yielded the nitroamine **16** and the diamine **17** upon removal of the protecting group. Diazotization of **15** also could be used as a route to halogen derivatives. Only the 4-iodo compound **18c** was prepared in this manner; the 4-chloro and 4-bromo materials **18a** and **18b** were more easily obtained by direct halogenation of **6a** in HOAc.

Attempts to utilize **8a** in the synthesis of **6c** proved fruitless. Reaction of **8a** with CH_3MgI[15] or with CH_3Li[16] gave predominantly recovered starting material, as did attempted Wittig reaction.[17] The isopropyl compound **6c** was therefore prepared by our previous method[2] from the requisite benzaldehyde.

Pharmacology and Discussion. In the first paper in this series,[2] **1a** was shown to improve avoidance acquisition in the rat. Recently, Tilson et al.[18] have demonstrated that **1a** facilitated avoidance behavior in rats without any obvious signs of stimulation, thus differentiating **1a** from (*R*)-DOM [(*R*)-**2a**] and (*S*)-amphetamine. In the present work, analogues of **1** (Table V) were screened in a cat behavior model[19] and selected compounds were then compared with **1a** in avoidance acquisition.[18]

The initial screening involved gross behavioral observation for "DOM-like" effects in cats. This test is a modification of that described by Wallach et al.[19] and consists of 12 behavior categories, each of which may receive a maximum numerical score of 2. The effects produced by **1** isomers were compared with those caused by (*R*)-DOM, (*R*)-DOET, and (*R*)-DOB. In this cat test, (*R*)-DOM was distinctively different from amphetamine as reported by Wallach[19] and observed in our laboratory.

The results obtained for **1** and analogues are listed in Table V. The *R* isomers of the reference phenylisopropylamines (Table V, footnote *i*) **2** show high activity in this model at relatively low doses (1 mg/kg or less). Potencies of the *S* isomers in this reference series were observed to be consistently lower than those of the corresponding *R* isomers. In contrast to the **2** series, **1** and analogues exhibited very low activity even at the relatively high screening dose (10 mg/kg) employed. Although most of the target compounds show some indication of activity, none of them approached (*R*)-DOM or other reference agents. Furthermore, differences between *R* and *S* isomers were not marked, perhaps because of the low intrinsic potencies observed with **1** analogues. Thus, the whole series could be considered to have relatively low hallucinogenic potential on the basis of this cat model. In clinical trials (Bristol Laboratories files), **1a** failed to produce any hallucinations at relatively high doses.

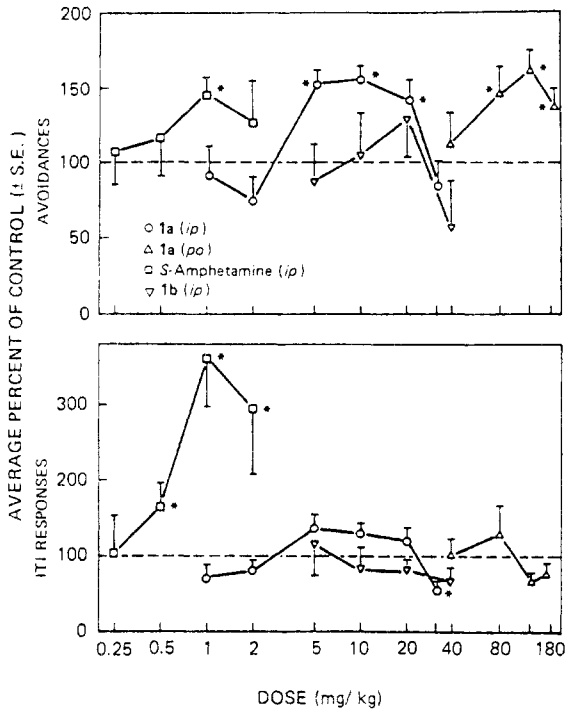


Figure 1. The effects of **1a** (ip and po), **1b** (ip), and (*S*)-amphetamine (ip) on the acquisition of shuttle box responding by naive, retired breeder rats. Data are average percentages (±SE) of control for 8–14 rats per group. Control avoidances per 120 trials for **1a** (ip) and (*S*)-amphetamine were 49.0 ± 4.4 (mean ± SE; $N = 36$), while the control values for **1a** (po) and **1b** (ip) were 40.9 ± 6.5 ($N = 16$) and 46.3 ± 5.5 ($N = 24$), respectively. ITI shuttles in 120 trials were 59.5 ± 7.7, 47.2 ± 7.2, and 40.0 ± 11.3 for **1a** (ip) and (*S*)-amphetamine (ip), **1a** (po), and **1b** (ip), respectively. Asterisks denote statistical difference from vehicle control ($p < 0.05$).

For information on potentially useful activity, a rat avoidance acquisition model was used.[18] Compound **1a** produced significant increases in avoidance response at 5, 10, and 20 mg/kg ip (Figure 1); the minimal effective dose (MED, Table VI) was 5 mg/kg. Significant changes in ITI (intertrial interval) responses following 1–20 mg/kg of **1a** were not observed. The highest dose of **1a** (30 mg/kg ip) tended to suppress avoidance response and significantly decreased the number of responses during the ITI. Orally administered **1a** was considerably less potent (MED, 80 mg/kg) than when given ip. The *S* isomer, **1b**, failed to produce any significant activity (MED >40 mg/kg ip).

Comparative data (Figure 1) on (*S*)-amphetamine revealed that it tended to enhance avoidance responses at 0.25–2 mg/kg ip, but only the effect at 1 mg/kg was statistically significant. (*S*)-Amphetamine differed from **1a** and **1b** in that amphetamine markedly stimulated ITI activity at 0.5–2 mg/kg. For a more detailed comparison between **1a**, (*S*)-amphetamine, and (*R*)-DOM, consult ref 18. In general, (*R*)-DOM (0.5–5 mg/kg ip) exhibited a

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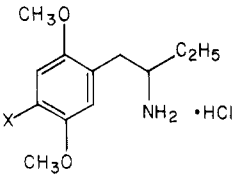
(17) G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961).
(18) H. A. Tilson, J. H. Chamberlain, and J. A. Gylys, *Psychopharmacology (Berlin)*, **51**, 169 (1977).
(19) M. B. Wallach, E. Friedman, and S. Gershon, *J. Pharmacol. Exp. Ther.*, **182**, 145 (1972).

Table VI. Relative Potency of 1a Analogues in the Rat Avoidance Acquisition Test



compd	X	MED,[a] mg/kg ip	potency rel to 1a	ITI act.
(*R*)-9a	*n*-Pr	1	5	↑[b]
(*R*)-6b	Et	2	2.5	↑
(*R*)-18b	Br	2	2.5	↑
1a	Me	5	1	NE[c]
(*R*)-6d	SMe	5	1	↑
(*R*)-18a	Cl	20	0.25	NE
(*R*)-9b	*n*-Bu	>20	<0.25	NE
(*R*)-6c	*i*-Pr	>20	<0.25	NE

[a] A minimal dose producing a significant ($p < 0.05$ vs. vehicle control) increase in avoidance responding. [b] Statistically significant increase. [c] No statistically significant effect.

biphasic response on avoidance acquisition, facilitating at 0.5 mg/kg ip and disrupting at 1 or 5 mg/kg ip. (*R*)-DOET [(*R*)-**2b**] failed to produce any positive effect over a wide dose range (0.25–5 mg/kg ip); in fact, there was an inhibitory effect at 1 and 5 mg/kg. The corresponding *S* isomers of DOM and DOET were considerably weaker or inactive in affecting avoidance acquisition at doses up to 10 mg/kg ip.

Selected 4-substituted analogues of **1a** were tested in avoidance acquisition, and the results are summarized in Table VI. The following selection criteria, based mainly on findings in the **2** series,[6] were used: (a) high biological potency of *R* forms as compared with the corresponding *S* isomer; (b) high biological activity of 4-halo analogues and selected 4-alkyl substituents. Selection of *R* isomers was also supported by higher activity of **1a** vs. **1b** in the avoidance acquisition test (Figure 1). Substitution of an ethyl [(*R*)-**6b**] or *n*-propyl [(*R*)-**9a**] for the methyl group of **1a** resulted in compounds that facilitate avoidance at 2–5 and 1–10 mg/kg ip, respectively. Facilitation of avoidance, however, was often accompanied by significant increases in ITI activity, particularly with the ethyl analogue (*R*)-**6b**. Other alkyl compounds tested included those having a 4-*n*-butyl or 4-isopropyl [(*R*)-**9b** and (*R*)-**6c**, respectively] substitution. Neither of these compounds demonstrated significant activity at doses up to 20 mg/kg ip. 4-Bromo substitution [(*R*)-**18b**] resulted in a compound that facilitated avoidance at 2 and 5 mg/kg. (*R*)-**18b** appeared more stimulating than **1a**, as indicated by the concomitant increases in ITI activity. The chloro analogue, (*R*)-**18a**, appeared less active than the bromo compound of this series, as indicated by the relatively high MED of 20 mg/kg. Substituting a 4-(methylthio) group [(*R*)-**6d**] also produced a behaviorally active substance, which had a MED of 5 mg/kg ip. Significant increases in avoidances, as well as ITI responses, were observed at 20 mg/kg.

As had previously been noted in the phenylisopropylamine series[6] (**2**), there appears to be a structural optimum regarding the 4-substituent in the phenyl-*sec*-butylamine series (**1a** and analogues) with respect to the activity in the avoidance acquisition test. The order of potency observed was *n*-propyl > ethyl > methyl = methylthio, while *n*-butyl and isopropyl were not active up to 20 mg/kg (Table VI). The potency order for alkyl substituents was in good agreement with that noted in the **2** series using the rabbit hyperthermia test.[6] However, the halo substituents in the butane series are seemingly less potent relative to alkyl substituents, which is not in accord with the findings in the propane series. In addition, Aldous et al.[6] found only a slight potency difference between bromo and chloro analogues of the propane series, while the bromo compound is more potent than the chloro analogue in the butane series.

Since the data of Aldous et al.[6] agree well with what is known of the hallucinogenic potencies of 2-amino-1-(2,5-dimethoxy-4-substituted-phenyl)propanes,[3,6,20] it would appear that hallucinogenic potential of a given **2a** analogue is not necessarily predictive of relative activity of the corresponding **1** analogue in the avoidance acquisition test. It does appear that there is a correlation between activity seen in the cat DOM test and the rabbit hyperthermia test as reported by Aldous et al.[6]

In summary, a number of analogues of **1** have been prepared, many through a common, optically active intermediate. The majority of these compounds on the basis of a cat behavior model should be of low hallucinogenic potential. Avoidance acquisition studies of selected compounds in comparison with **1a** have shown five of these analogues [(*R*)-**6b**, (*R*)-**6d**, (*R*)-**9a**, (*R*)-**18a**, and (*R*)-**18b**] to produce statistically significant enhancement; three of these [(*R*)-**6b**, (*R*)-**6d**, and (*R*)-**18b**] were more potent than **1a**. However, these active analogues [with the exception of (*R*)-**18a**, the compound of lowest potency] produced significant increases in ITI responses. This is an indication of general CNS stimulation and thus possible stimulatory side effects. It is noteworthy that **1a** did not produce such increase at any of the dose levels tested.

It has been found that the potential performance-enhancing (avoidance test) activiy of **1a** may be increased by proper selection of a nuclear 4-substituent; the more potent compounds retain relatively low hallucinogenic liability (cat test). Also, the effect of a given nuclear 4-substituent upon hallucinogenic potency in the phenylisopropylamine series does not necessarily correspond to the effect of that substituent upon avoidance enhancement in our phenyl-*sec*-butylamine series.

Experimental Section

Chemistry. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Department of Bristol Laboratories. Where indicated by symbols of the elements, the analytical results obtained were within ±0.4% of the calculated values. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter using 1% solutions in 95% EtOH. GC analyses were performed on a F & M Model 810 gas chromatograph equipped with a flame-ionization detector. All products gave IR and NMR spectra consistent with their expected structures. The optical purity of all optical isomers listed in Table V was checked by the method previously detailed.[2] All such isomers showed optical purities of >98% by this technique.

2,5-Dimethoxy-4-(2-propyl)benzaldehyde.[6] (a) To a stirred solution, under N_2, of 0.33 mol of MeMgI in 100 mL of dry Et_2O was added dropwise a solution of 54 g (0.30 mol) of 2,5-dimethoxyacetophenone in 150 mL of dry Et_2O at such a rate as to maintain gentle reflux. After the addition was complete, the mixture was stirred and refluxed on the steam bath for 1.5 h. The reaction mixture was cooled and poured onto 300 mL of 10% H_2SO_4 and 300 g of crushed ice. The layers were separated and the aqueous layer was extracted thoroughly with Et_2O. The combined extracts were washed with H_2O, $NaHCO_3$ solution, and

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saturated brine and then dried (Na_2SO_4). Evaporation of the solvent gave ca. 62 g of a yellow oil.

This oil was dissolved in 500 mL of toluene; a catalytic amount of *p*-toluenesulfonic acid was added and the solution was stirred and refluxed under a Dean–Stark H_2O separator for 8 h. The dark solution remaining in the flask was evaporated under reduced pressure and the oil thus obtained was dissolved in 100 mL of 100% EtOH. Catalyst (10% Pd on carbon, 3 g) was added and the mixture was hydrogenated at an initial pressure of 3 atm. After 1 h, the calculated amount of H_2 had been absorbed and no further pressure drop occurred. The catalyst was filtered and the solvent evaporated. The residual oil was vacuum distilled to give 47.1 g (87%) of 2,5-dimethoxyisopropylbenzene as a colorless oil, bp 96–104 °C (4 mm).

(b) A mixture of 101 mL (1.10 mol) of $POCl_3$ and 117 mL (0.95 mol) of *N*-methylformanilide was stirred at ambient temperature for 1.5 h. 2,5-Dimethoxyisopropylbenzene (47.0 g, 0.26 mol) was then added portionwise, and the dark mixture was stirred and heated on the steam bath for 3.5 h. The mixture was cooled to 50 °C and the dark syrup was cautiously poured into 1 L of crushed ice and H_2O. The reaction flask was rinsed with two 100-mL portions of H_2O and 100 mL of 100% EtOH, and the rinses were added to the quench mixture. Upon stirring well and scratching, a solid began to separate. The mixture was stored at 0 °C (1.5 h) and the solid was then filtered. The filter cake was dissolved in ca. 350 mL of hot EtOH; the solution was filtered and the filtrate was diluted with 200 mL of H_2O. Upon standing at room temperature for 16 h, and then chilling for 30 min at 0 °C, the product separated as large tan needles, mp 69.5–73 °C. A second crop was obtained from the mother liquor. The total yield of the title compound was 46.9 g (85%), lit.[6] mp 70 °C.

1-[2,5-Dimethoxy-4-(2-propyl)phenyl]-2-nitro-1-butene (3c). A mixture of 6.36 g (30.6 mmol) of 2,5-dimethoxy-4-(2-propyl)benzaldehyde, 0.64 g (2.7 mmol) of *n*-butylamine, 3.14 g (35.2 mmol) of 1-nitropropane, and 10 mL of dry toluene was refluxed for 16 h without removal of H_2O. The reaction mixture was cooled and washed successively with H_2O, 5% HCl solution, H_2O, and saturated brine and then dried (Na_2SO_4).

Evaporation of the solution under reduced pressure gave 6.12 g of a dark red oil, which slowly crystallized. Recrystallization from pentane gave 4.14 g (48% yield) of the title compound as yellow crystals, mp 60.5–62.5 °C. Anal. ($C_{15}H_{21}NO_4$) C, H, N.

1-(2,5-Dimethoxy-4-methylphenyl)-2-nitro-1-butene[2] (Improved Procedure). 2,5-Dimethoxy-4-methylbenzaldehyde (10.0 g, 55.5 mmol) was mixed with 2.14 g (27.7 mmol) of NH_4OAc and 100 mL of 1-nitropropane, and the solution (upon heating) was refluxed for 20 h.

The H_2O formed in the reaction and excess nitropropane were evaporated under reduced pressure and the reddish-orange solid obtained (12.9 g) was washed thoroughly with H_2O and air-dried.

The crude product was recrystallized from 300 mL of MeOH to give 9.65 g of the title compound as orange crystals, mp 119–121 °C. A small second crop was obtained. The total yield was 10.16 g (72%).

Resolution of (±)-2-Amino-1-[2,5-dimethoxy-4-(methylthio)phenyl]butane (6d) Isomers. (a) *R* Isomer. A mixture of amine **6d** (31.3 g, 123 mmol) and 16.6 g (61.3 mmol) of (+)-2′-nitrotartranilic acid[11] was dissolved in 90 mL of hot MeOH. The solution was allowed to stand undisturbed at room temperature for 17 h and then was cooled at 4 °C for 4 h. The crystalline salt was filtered and washed with Et_2O. The mother liquor and washings were saved for recovery of the *S* isomer. The product was dried under vacuum to give 28.55 g (88.6% yield) of yellow crystals, mp 159–164 °C.

Recrystallization from 130 mL of MeOH, filtration, and washing with 100 mL of cold MeOH afforded 14.85 g (46.1% yield), mp 164–170 °C. A second recrystallization from 90 mL of MeOH gave 8.3 g (25.7% yield) of yellow crystalline salt, mp 171–173 °C. This salt was slurried in 200 mL of saturated $NaHCO_3$ solution and the free base was extracted with EtOAc. The combined extracts were washed with 5% $NaHCO_3$ solution and then with brine, dried (Na_2SO_4), and evaporated to give the free amine as a crystalline solid: yield 3.58 g; mp 60–63 °C; $[\alpha]^{24}_{365}$ -164.2° (*c* 1.0, 95% EtOH).

The amine was dissolved in 100% EtOH and the salt formed with HCl (g). Ether was added and the solid was filtered, washed with Et_2O, and dried under high vacuum: yield 3.7 g; mp 247–251 °C. Two recrystallizations from 100% EtOH provided 1.22 g (11%) of pure (*R*)-**6d**·HCl: mp 254–256 °C; $[\alpha]^{24}_{365}$ -76.3° (*c* 1.0, 95% EtOH). Anal. ($C_{13}H_{21}NO_2S$·HCl) C, H, N, Cl. A sample of HCl salt converted to free base had mp 64–65 °C and $[\alpha]^{24}_{365}$ -210.9° (*c* 1.0, 95% EtOH).

(b) *S* Isomer. The mother liquor from isolation of the *R* isomer was evaporated to dryness and the residue converted to the free base as described in part a. The residue (16.8 g, 61.8 mmol) and 11.7 g (43.3 mmol) of (−)-2′-nitrotartranilic acid[11] were dissolved in 95 mL of hot 95% EtOH. The solution was cooled, seeded with salt previously obtained on a test-tube scale, and allowed to stand undisturbed at room temperature for 5 h. The solid was filtered, washed with cold 95% EtOH, and dried under high vacuum to give 20.3 g (89%) of salt, mp 164–168 °C.

Recrystallization from 125 mL of 95% EtOH as described in part a afforded 15.7 g (69%) of salt, mp 168–172 °C. A second recrystallization from 100 mL of 95% EtOH gave 12.4 g (55%) of the pure (−)-2′-nitrotartranilic acid salt of (*S*)-**6d**, mp 171–174 °C.

The salt was dissolved in 150 mL of hot H_2O and converted to the free base with excess K_2CO_3. Cooling gave the free amine as a colorless crystalline mass. Filtration and washing with cold H_2O, followed by drying under high vacuum, afforded 6.1 g, mp 50–64 °C. The free amine was dissolved in 100% EtOH and the salt was formed with HCl (g). Addition of Et_2O gave 6.41 g (36%) of HCl salt, mp 247–253 °C. Recrystallization from 100% EtOH and washing with cold EtOH and then with Et_2O afforded 5.3 g (29%) of pure (*S*)-**6d**·HCl: mp 254–256 °C; $[\alpha]^{24}_{365}$ +79.9° (*c* 1.0, 95% EtOH). Anal. ($C_{13}H_{21}NO_2S$·HCl) C, H, N, Cl. A sample of HCl salt converted to free amine had mp 64–67 °C and $[\alpha]^{24}_{365}$ +214.8° (*c* 1.0, 95% EtOH).

(*R*)-1-(2,5-Dimethoxyphenyl)-2-(*N*-phthalimido)butane [(*R*)-7]. Procedure A. A solution of 8 g (80.0 mmol) of dry triethylamine and the oily free base obtained from 19.6 g (80.0 mmol) of (*R*)-**6a**·HCl in 250 mL of toluene was stirred with 12.3 g (80.0 mmol) of phthalic anhydride; a slight exotherm occurred and solution was attained. Upon refluxing this solution for 16 h under a Dean–Stark trap, the theoretical quantity of H_2O separated. The solution was cooled and washed with 10% HCl, H_2O, 10% NaOH, H_2O, and saturated brine and dried (Na_2SO_4). The solvent was evaporated and the residue was stripped at 75 °C (0.05 mm) to give 27.1 g (100% yield) of a thick oil, $[\alpha]^{25}_{D}$ -183.2° (*c* 1.0, 95% EtOH), which showed a single sharp peak on GC. Anal. ($C_{20}H_{21}NO_4$) C, H, N.

(*R*)-1-(2,5-Dimethoxy-4-propionylphenyl)-2-(*N*-phthalimido)butane [(*R*)-8b]. Procedure B. To a stirred solution of 10.2 g (30 mmol) of (*R*)-**7** in 250 mL of dry CH_2Cl_2, at −20 °C, was added dropwise 6.15 mL (56 mmol) of $TiCl_4$. Propionyl chloride (2.15 mL, 35 mmol) was then added dropwise and the dark solution was stirred at −20 °C for 30 min. Stirring was continued at ambient temperature for 77 h.

The dark solution was vigorously shaken with 250 mL of ice–H_2O; the layers were separated and the aqueous layer was extracted well with CH_2Cl_2. The combined extracts were washed with H_2O, diluted HCl, H_2O, saturated $NaHCO_3$ solution, and saturated brine and then dried (Na_2SO_4). Evaporation of the solvent gave a yellow oil which crystallized upon standing. This was recrystallized from EtOH to give the title compound as colorless, fibrous needles: mp 112–113 °C; yield 7.25 g (61%). Anal. ($C_{23}H_{25}NO_5$) C, H, N.

(*R*)-2-Amino-1-[2,5-dimethoxy-4-(1-propyl)phenyl]butane Hydrochloride [(*R*)-9a]. Procedure C. To a solution of 4 g (10 mmol) of (*R*)-**8b** in 100 mL of glacial HOAc was added 20 drops of 60% aqueous $HClO_4$ solution and 1.5 g of 10% Pd on carbon catalyst; the mixture was hydrogenated at 3 atm for 3 h. The catalyst was filtered and washed with CH_2Cl_2. The filtrate was shaken with H_2O and the organic layer was separated. The aqueous layer was extracted with 3 portions of Et_2O; the combined organic solutions were washed well with H_2O, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Evaporation of the solvents gave 3.79 g of crude (*R*)-1-(2,5-dimethoxy-4-*n*-propylphenyl)-2-(*N*-phthalimido)butane as a green oil, 87% pure by GC.

A solution of the crude phthalimido compound (3.75 g, 8.5 mmol) and 3 mL (94.6 mmol) of 95% hydrazine in 100 mL of

100% EtOH was stirred and refluxed for 2 h and then stood at ambient temperature for 16 h. The solvent was removed under reduced pressure and excess N_2H_4 was chased with 2 portions of toluene. The solid was stirred for 1.5 h with 10% HCl; the resulting slurry was warmed on the steam bath and filtered. The filtrate was made basic with NaOH solution and extracted with 4 portions of Et_2O. The combined extracts were washed with H_2O and saturated brine and dried (Na_2SO_4). An excess of HCl (g) in dry Et_2O was added; the salt slowly separated. The mixture was chilled at 0 °C for 1 h and then filtered. The salt was recrystallized from MeCN to give 2.0 g (75% yield) of the title compound as a colorless solid: mp 174.5–176.5 °C; $[\alpha]^{23.5}_D$ −10.9° (c 1.0, 95% EtOH). Anal. ($C_{15}H_{25}NO_2$·HCl) C, H, N, Cl.

1-(2,5-Dimethoxy-4-formylphenyl)-2-(*N*-phthalimido)butane (10). Procedure D. (a) *R* Isomer. A stirred solution, under N_2, of 9.2 g (27 mmol) of (*R*)-**7** in 75 mL of dry CH_2Cl_2 was maintained at 0 °C while 5 mL (8.63 g, 45 mmol) of $TiCl_4$ was added dropwise. α,α-Dichloromethyl methyl ether (3.1 g, 27 mmol) was then added, dropwise, at 0 °C. The reddish-brown solution was stirred at 0 °C for 30 min; the temperature was then raised to 25 °C over a period of 15 min. The solution was then stirred at 35 °C for 15 min and then refluxed for 15 min. The warm reaction mixture was then poured into 200 mL of ice–H_2O. The mixture was shaken vigorously, the layers were separated, and the aqueous layer was extracted with 3 portions of CH_2Cl_2. The combined organic solutions were washed with H_2O and saturated brine and dried (Na_2SO_4). Removal of the solvent gave 9.6 g of green oil which crystallized upon seeding. Recrystallization from MeOH–H_2O gave 6.36 g (64% yield) of (*R*)-**10** as colorless crystals: mp 111–113 °C; $[\alpha]^{24.8}_D$ −258.6° (c 1.0, 95% EtOH). Anal. ($C_{21}H_{21}NO_5$) C, H, N.

The product was initially obtained crystalline by chromatography of 2.0 g of the crude oil on 150 g of neutral silica gel. The column was eluted with Skellysolve B containing increasing proportions of CH_2Cl_2 and finally with pure CH_2Cl_2. Evaporation of the combined fractions containing the compound first eluted gave 1.35 g (67%) of an oil which crystallized upon standing.

(b) Racemic Isomer. This material was prepared by the procedure described in part a from 35.7 g (105 mmol) of (±)-**7** and proportionate quantities of other reagents. The crude, oily product was chromatographed on 1 kg of Woelm activity III neutral alumina, eluting with Skellysolve B containing increasing proportions of CH_2Cl_2 (5, 10, 15, 25, and finally 50%). The product began to appear in fractions containing 25% CH_2Cl_2. The fractions were combined and solvents evaporated to give 21.61 g of an oil. This was dissolved in 150 mL of hot 95% EtOH and the solution was incubated at room temperature for 24 h and then at −15 °C for 48 h. Large, pale green crystals were obtained: yield 15.97 g (43%); mp 92–96 °C. Anal. ($C_{21}H_{21}NO_5$) C, H, N.

(*R*)-1-(2,5-Dimethoxy-4-hydroxyphenyl)-2-(*N*-phthalimido)butane [(*R*)-11]. Procedure E. To a stirred solution of 10.0 g (27.2 mmol) of (*R*)-**10** in 200 mL of $CHCl_3$ was added, all at once, 6.92 g (34.1 mmol) of 85% *m*-chloroperoxybenzoic acid. The resulting solution was stirred at room temperature for 22 h. The solution was concentrated under reduced pressure until a solid began to separate. The residual mixture was taken up in Et_2O and the solution was washed with dilute $NaHSO_3$ solution (2 portions). The solvent was evaporated to give 10.4 g of the formyloxy compound as an amber resin.

The crude ester was dissolved in 200 mL of 100% EtOH, and HCl (g) was bubbled through the solution for 15 s. The flask was then sealed and the solution stood at room temperature for 18 h. The solvent was evaporated and traces of HCl were chased with 2 portions of 95% EtOH. The crude solid was recrystallized from *i*-PrOH to give 6.77 g (70% overall) of (*R*)-**11** as crystals: mp 123–125 °C; $[\alpha]^{23}_D$ −176.2° (c 1.0, 95% EtOH).

(*R*)-2-Amino-1-(2,5-dimethoxy-4-ethoxyphenyl)butane Hydrochloride [(*R*)-13a]. Procedure F. To a stirred solution of 2.0 g (5.63 mmol) of (*R*)-**11** in 50 mL of dry DMF was added 0.253 g (6.0 mmol) of 57% NaH in mineral oil. After gas evolution had ceased, a solution of 0.97 mL (1.87 g, 12.0 mmol) of iodoethane in 10 mL of dry DMF was added dropwise. The solution was stirred at room temperature for 30 min, at 45–55 °C for 1.5 h, and then at ambient temperature for 16 h.

The DMF was removed under reduced pressure and the residue was partitioned between Et_2O and H_2O. The layers were separated and the aqueous layer was extracted with 2 portions of Et_2O. The combined organic solutions were washed with 5% NaOH solution (3 portions) and H_2O (3 portions), dried, and evaporated.

The oil thus obtained and 2.13 mL (2.15 g, 67.2 mmol) of 95% hydrazine were dissolved in 100 mL of 100% EtOH, and the solution was stirred and refluxed for 5 h and then stirred at ambient temperature for an additional 14 h. The mixture was evaporated under reduced pressure and residual N_2H_4 was chased with 2 portions of 95% EtOH. The residue was triturated with 5% HCl; the solid was filtered and the filter cake was washed with 5% HCl and then with H_2O. The filtrate was made basic with NaOH solution and the oil was extracted with Et_2O. The combined extracts were washed well with H_2O, dried ($MgSO_4$), and evaporated. The oily residue was taken up in dry Et_2O and the salt was formed with HCl (g). The product slowly separated as a yellow powder. The mixture was chilled at −15 °C and filtered. The crude salt was recrystallized from acetone to yield 0.81 g (59% yield) of the title compound: yellow crystals; mp 189–190.5 °C; $[\alpha]^{23}_D$ −13.9° (c 1.0, 95% EtOH). Anal. ($C_{14}H_{23}NO_3$·HCl) C, H, N, Cl.

(*R*)-1-(2,5-Dimethoxy-4-nitrophenyl)-2-(*N*-phthalimido)-butane [(*R*)-14]. To a stirred solution of 16.2 g (47.7 mmol) of (*R*)-**7** in 270 mL of glacial HOAc was added, all at once, 14.1 mL (20.1 g, 223 mmol) of concentrated HNO_3 in 120 mL of H_2O. The solution was stirred at room temperature for about 4 h, darkening during this time to a reddish-orange color. The solution was then poured into 1 L of cold H_2O; the product separated as a yellow gum which crystallized within 30 min. This material was filtered, washed well with H_2O, air-died, and then recrystallized from 95% EtOH to give 16.35 g (90%) of (*R*)-**14** as yellow crystals: mp 140.5–142.5 °C; $[\alpha]^{23}_D$ −224.8° (c 1.1, $CHCl_3$). Anal. ($C_{20}H_{20}N_2O_6$) C, H, N.

(*R*)-1-(4-Amino-2,5-dimethoxyphenyl)-2-(*N*-phthalimido)butane [(*R*)-15]. A suspension of 12.6 g (32.8 mmol) of the nitro compound (*R*)-**14** and 4.0 g of 10% Pd on carbon catalyst in 200 mL of 100% EtOH was hydrogenated at an initial pressure of 3 atm. Pressure drop was rapid and heat was evolved. The hydrogenation was continued for 16 h.

The pressure drop was 107% of the calculated value. The solids were filtered and the filter cake was washed with CH_2Cl_2 until the washings were colorless. The filtrate was evaporated to give an amber solid, which was recrystallized from 50% aqueous EtOH to provide 10.46 g (90%) of the title compound as glistening amber crystals: mp 141–142.5 °C; $[\alpha]^{24}_D$ −197.6° (c 1.0, $CHCl_3$). Anal. ($C_{20}H_{22}N_2O_4$) C, H, N.

(*R*)-2-Amino-1-(4-amino-2,5-dimethoxyphenyl)butane [(*R*)-17]. Procedure G. To a stirred, hot solution of 2.0 g (5.65 mmol) of (*R*)-**15** in 120 mL of 100% EtOH was added all at once 2.0 mL (2.02 g, 63.1 mmol) of 95% hydrazine. Stirring and refluxing was maintained for 5 h; separation of phthalhydrazide was observed within 90 min. The reaction mixture was then stirred at room temperature overnight (14 h).

The mixture was evaporated and residual N_2H_4 was chased with 2 portions of EtOH. The residue was then triturated with 5% HCl solution and the resulting suspension was filtered. The filter cake was washed with 5% HCl (1 portion) and H_2O (2 portions), and the filtrate and washings were combined and made basic (pH 9) with 40% NaOH solution. The insoluble material was extracted with 3 portions of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated.

The residual solid was recrystallized from ca. 200 mL of H_2O to give 0.824 g (65%) of product as fluffy, amber needles: mp 79–80 °C; $[\alpha]^{23.5}_{365}$ −210.1° (c 1, 95% EtOH). Anal. ($C_{12}H_{20}N_2O_2$) C, H, N.

(*R*)-2-Amino-1-(4-bromo-2,5-dimethoxyphenyl)butane Hydrochloride [(*R*)-18b]. Procedure H. To a stirred solution of (*R*)-**6a** [obtained from 20.0 g (81.6 mmol) of the corresponding hydrochloride] in 150 mL of glacial HOAc was added dropwise, at −10 °C, a solution of 13.1 g (82 mmol) of Br_2 in 50 mL of glacial HOAc. After the addition was complete, the solution was stirred at −10 °C for 1 h; the reaction mixture solidified. The cooling bath was removed and the reaction mixture stood at room temperature for 40 h.

The mixture was diluted with 150 mL of Et_2O and allowed to stand for 2 h. The white solid was filtered, washed with Et_2O, and dried to give 22.65 g of the hydrobromide salt of the product.

The hydrobromide was converted to the free base and the salt was formed with HCl (g) in dry Et_2O. The crude material was recrystallized from *i*-PrOH to give 18.8 g (71%) of the title compound as colorless crystals: mp 240–242 °C; $[\alpha]^{24}_{365}$ −58.0° (*c* 1.0, 95% EtOH). Anal. ($C_{12}H_{18}BrNO_2$·HCl) C, H, N.

(*R*)-2-Amino-1-(2,5-dimethoxy-4-iodophenyl)butane Hydrochloride [(*R*)-18c]. Concentrated HCl (3.52 mL, 42.3 mmol) was added all at once to a hot, stirred solution of 5.0 g (14.1 mmol) of (*R*)-**15** in 200 mL of 100% EtOH. The darkened solution was cooled rapidly to 15 °C. Water (120 mL) was added (a gelatinous precipitate dissolved) and the solution was cooled to 2–3 °C and maintained at this temperature while a solution of 1.07 g (15.51 mmol) of $NaNO_2$ in 20 mL of H_2O was added dropwise with stirring. After 40 min, a solution of 2.57 g (15.51 mmol) of KI in 20 mL of H_2O was added dropwise with stirring to the reaction mixture; a dark red-brown semisolid began to separate.

Stirring was continued at 2–3 °C for 3 h. The cooling bath was then removed and stirring continued for an additional 2 h; the temperature of the reaction mixture had risen to 20 °C. The temperature was then held at 40–50 °C for 30 min. The dark reaction mixture was diluted with an equal volume of H_2O and extracted with 3 portions of Et_2O. The combined extracts were washed successively with 2 portions of 10% $NaHSO_3$, 5% HCl, 5% NaOH, and finally H_2O (3 portions). The Et_2O solution was dried ($MgSO_4$) and evaporated to give 2.91 g of dark red oil.

The crude material was chromatographed on 300 g of activity III alumina. Elution was with 25% CH_2Cl_2 in Skellysolve B and progress was followed by TLC (alumina, 1:1 CH_2Cl_2–Skellysolve B, visualization with shortwave UV). The material first eluted was (*R*)-1-(2,5-dimethoxy-4-iodophenyl)-2-(*N*-phthalimido)butane: yield 1.06 g (16%) of clear, yellowish oil 97% pure by GC.

Without further purification, the phthalimido compound was hydrazinolyzed as described for (*R*)-**13a**. The crude hydrochloride salt of the product was recrystallized from *i*-PrOH to give 0.376 g (44%) of colorless needles: mp 255.5–257 °C dec; $[\alpha]^{24}_{365}$ −56.8° (*c* 1.0, 95% EtOH). Anal. ($C_{12}H_{18}INO_2$·HCl) H, N, I; C: calcd, 38.78; found, 39.27.

Pharmacology. Cat Behavior. This procedure represents a modification of that described by Wallach et al.[19] Adult female cats were placed in separate cages approximately 12–15 sq ft in floor area. The animals could see the experimenter and each other across the room and could have auditory and olfactory contact among themselves in adjacent cages.

After animals had become accustomed to this environment (30 min), test compounds were administered subcutaneously into the back of the neck. Following dosing, animals were observed for 3 h. Scoring was done at the time of peak drug-induced effects, usually about 1 h postdosing. The effects were scored using an observational checklist consisting of 12 categories, each containing 2 items. Each item was worth 1 point, with a maximum total numerical score of 24. A total score of 10 or greater was considered "DOM-like".

The categories were: body posture, arched back/stiff tail; extension of limbs, legs/legs and toes; muscle rigidity, legs/abdomen, abnormal leg/immobility; motor coordination, ataxia/loss of righting reflex, open mouth/protruding tongue, claws out/attempts to bite or claw, teeth baring/hissing or growling; contact with environment, reduced/absent; piloerection, tail/back; pupillary constriction, moderate/extreme; salivation/emesis.

Either two or four animals were used per test. For $N = 2$, an average of the individual scores was taken. For $N = 4$, means plus or minus standard error were reported.

Avoidance-Response Acquisition. Male, retired breeder rats of the Long–Evans strain (Blue Spruce Farms, 600–800 g) were given 120 massed acquisition trials in a shuttle box (BRS/LVE, Model 146-04) as described elsewhere.[18] Briefly, each trial was 30 s in duration and consisted of a 5-s light (conditioned stimulus, CS) presented on the side of the shuttle cage occupied by the subject. If the rat did not cross to the other side of the chamber within the 5-s CS period (avoidance response), the grid floor under the animal was electrified with 0.8 mA of scrambled shock (BRS/LVE, Model 1531 shocker). The animal was permitted 5 s to make an escape response before termination of the light and shock stimuli. Avoidance responses turned the CS off, while an escape response terminated both the CS and the shock. Either response initiated the intertrial interval (ITI), which was 20–30 s, depending on the response of the subject during the CS or shock periods. Responses during the ITI were taken as a measure of nonspecific motor activity and were not punished. Drugs were dissolved in a distilled water vehicle and injected ip 5–10 min or administered by intragastric gavage (po) 30 min prior to the 1-h behavioral test. Differences between the means of control and drug groups were tested for statistical significance by a Student's *t*-test. The accepted level of significance was set at $p < 0.05$. Potency differences between some of the drugs were determined by comparing the minimal effective doses (MED) required to increase avoidance responding significantly (see Table VI). The MED was established by evaluating a set order of doses within the 0.25–20 mg/kg ip range (i.e., 5, 2, or 10, 1 or 20, followed by 0.5, 30, or 40 mg/kg, if necessary).

Synthesis and Analgesic Activity of Some 14β-Substituted Analogues of Morphine

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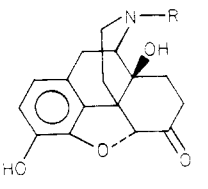
Treatment of 14β-nitrocodeinone with sodium borohydride gave the codeine derivative which was reduced with zinc dust in acetic anhydride–acetic acid solution to give 14β-acetamidocodeine 6-acetate. 14β-Thiocyanatocodeinone was obtained from the reaction of thebaine with thiocyanogen and was reduced to 14β-mercaptocodeine with lithium aluminum hydride. 14β-Bromo- and 14β-chlorocodeinone were prepared by the reaction of thebaine with *N*-bromosuccinimide and *N*-chlorosuccinimide, respectively. These 14β-substituted codeine and codeinones were O-demethylated to the corresponding morphine analogues with boron tribromide. With the exception of 14β-nitromorphinone, which was weak in activity, all the other 14β-substituted morphine derivatives were approximately equal in potency to normorphine in the guinea pig ileum preparation.

The substitution of hydroxyl groups at the 14β position of the morphine skeleton has produced compounds possessing significant pharmacological activities. Oxymorphinone (1, R = CH_3) is approximately ten times as potent as morphine sulfate as a narcotic analgesic[1] and naloxone (1, R = $CH_2CH{=}CH_2$) is a useful narcotic antagonist which possesses no agonist properties in humans.[2]



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Other than such compounds having oxygen functionalities at the 14β position, there is a paucity of analogues of morphine bearing other functional groups at this position.[3]

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