tected with a drying tube. A solution of phosgene (55 ml, 12.5% in benzene) was then added with vigorous stirring. The reaction was cooled for an additional 10 min and was then kept at room temperature for 1 hr. The reaction mixture was cooled again, treated with 100-ml portions of 1 *N* HCl until free of amine, and then rinsed successively with 8% $NaHCO_3$ and water, dried, and evaporated, giving a thick oil which solidified in methanol. Recrystallization from 95% ethanol to give a crystalline product, 1.08 g (46.5%), mp 110–113°. *Anal.* ($C_{21}H_{15}F_6NO_2 \cdot H_2O$) C, H, N.

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Structure–Activity Relationships in Psychotomimetic Phenylalkylamines

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A study has been made of the relationship between the structure of phenylalkylamines and potential correlates of their psychotomimetic activity. Optimum activity is associated with (a) an isopropylamine side chain, with a *R*-(−) configuration at the carbon atom α to the amino group, and (b) 2,5-dimethoxy substitution, together with an alkyl or halo group at position 4 that is probably limited in bulk to *n*-propyl or bromo. The activity of compounds in producing hyperthermia in rabbits provides good quantitative correlation with reported psychotomimetic activities in man.

Phenylalkylamines, and in particular phenylisopropylamines or amphetamines, are one of the few types of psychotomimetic compound for which extensive structure–activity relationships (SAR) are available.[1] Many of them have been tested in man[2] but, while a variety of procedures has been used such as disruption of conditioned avoidance responses (CAR) in rats[3,4] and inhibition of swim-maze performance in mice,[5] there is no wholly satisfactory animal testing procedure which allows quantitative comparison of relative potencies. The latter is especially important where enantiomeric potency ratios are concerned, though it is claimed that clinical observation in man[6] or CAR in rats[7] provides sufficient delineation of the psychotomimetic activities of the *R* and *S* enantiomers of the 2,5-dimethoxy-4-methyl derivative of amphetamine (DOM, STP). Furthermore, a correlation apparently exists between the smooth muscle stimulating activity of phenylisopropylamines and their known psychotomimetic activity in man.[8] We report SAR in psychotomimetic phenylalkylamines, using pharmacological methods which we believe provide a more reliable and accurate measure of relative potencies. Our study includes the effects upon activity of both ring substitution and variation in the alkylamine side chain.

Chemistry. Phenylisopropylamines containing different ring substituents were prepared by the classical route of Knoevenagel condensation between the appropriate benzaldehyde and nitroethane, followed by $LiAlH_4$ reduction.[5] Their homologs, the 3-amino-1-phenylbutanes, were obtained by oximation and reduction of the corresponding 1-phenylbutan-3-ones. Both cis and trans isomers of various 2-phenylcyclopropylamines were derived from the same synthetic sequence, Curtius transformation of the mixed ester from reaction of the appropriate styrene with ethyl diazoacetate;[9] solely trans isomers were also obtained from the trans ester resulting from reaction between *trans*-cinnamates and dimethylsulfoxonium methylide.[10] Other side-chain variations based on the 2,5-dimethoxy-4-methylphenyl skeleton involved successive alkyla-

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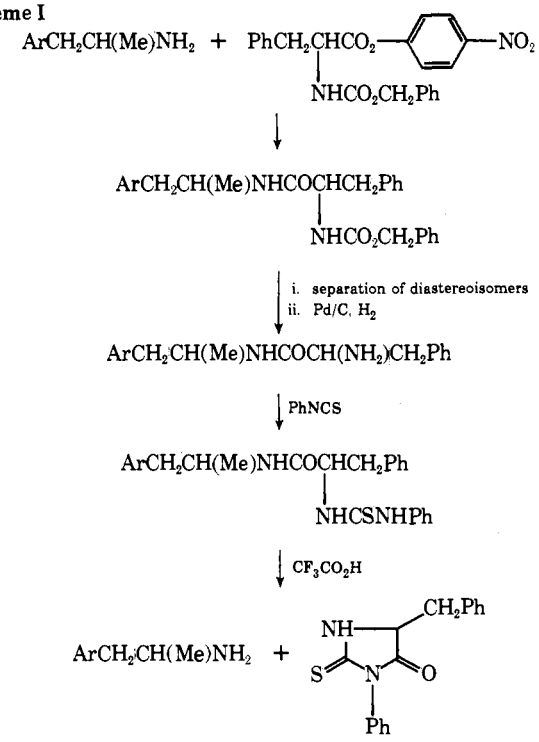
†This paper is dedicated to my former mentor and colleague, Alfred Burger.

tion and reduction of the appropriate phenylacetonitriles.[11]

Those enantiomeric phenylisopropylamines which have been previously studied for their psychotomimetic activity[6-8] were prepared by hydrogenation and hydrogenolysis of the condensation product from a 1-phenylpropan-2-one and (+)- or (−)-α-methylbenzylamine.[12] Our resolution (Scheme I) involved reaction of the phenylisopropylamine with *N*-benzyloxycarbonyl-L- (or D-) phenylalanine *p*-nitrophenyl ester, separation of the diastereoisomeric amides by fractional crystallization, and recovery of the enantiomeric phenylisopropylamines by catalytic hydrogenation followed by Edman degradation.[13] Conformations were assigned on the basis of the chemical shifts of the doublet due to the α-methyl group of the amides,[14,15] the *R*-(−) isomer giving signals at τ 9.08 and 9.15, the *S*-(+) isomer at τ 8.96 and 9.03.

Scheme I



Pharmacology. Phenylalkylamines resemble other psychotomimetic drugs in possessing not a single type of activity but rather a variable spectrum of pharmacological properties. Amphetamine, for example, is often regarded mainly as a central stimulant though it has anorectic properties in addition to effects upon the cardiovascular system and thermoregulatory processes. Manipulation of the structure of amphetamine can increase or decrease any one or several of these properties;[16] amphetamine itself is psychotomimetic only on chronic administration,[17] whereas DOM has outstanding psychotomimetic properties though it still retains some amphetamine-like properties such as the cardiovascular effects.[18]

The pharmacological evaluation of the present compounds was therefore designed to distinguish between psychostimulant (amphetamine-like) and psychotomimetic (LSD-like) activities. Initially, the ability to produce hyperthermia in rabbits was used as a qualitative screen for the detection of possible psychotomimetic activity, although it is known that this test also detects compounds which will prove lacking in such activity on further evaluation.[19] Nevertheless, this method provides a reliable quantitative measure of relative potencies once a compound has been shown by additional tests to be mainly LSD-like rather than merely amphetamine-like. Furthermore, it has the advantage over other widely used methods, such as behavioral responses in rodents[3-5] and cats[20] or the production of head twitches[21] or scratching[22] in mice, in that it permits monitoring of the time-course of drug action (Figures 1 and 2).

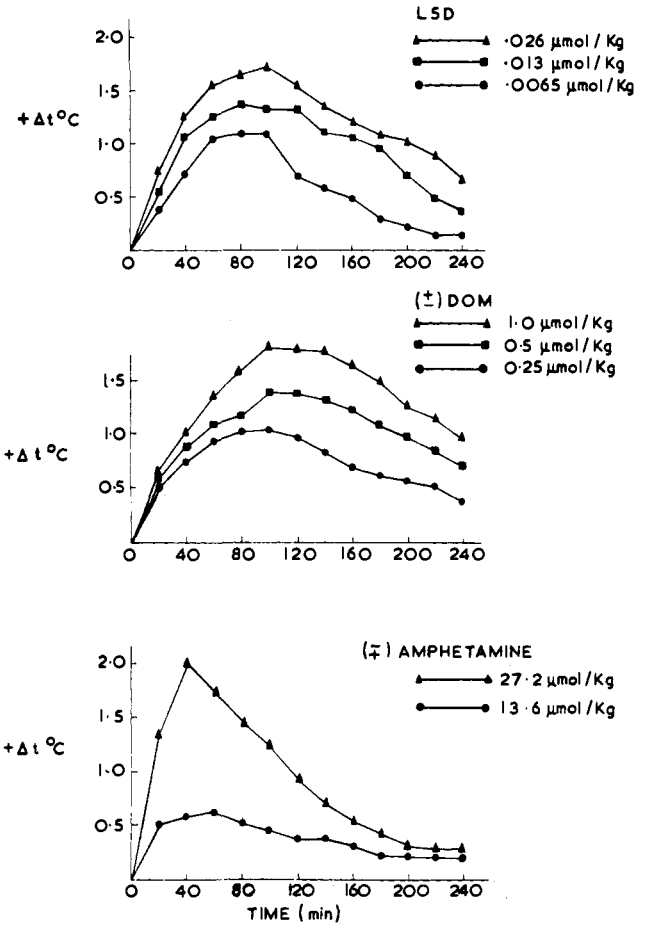


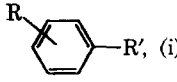
Figure 1. Time-activity profile of induced hyperthermia in rabbits produced by LSD, (±)-DOM, and (±)-amphetamine. Maximum standard errors of mean are indicated in Table I.

Additional tests to confirm that a compound producing hyperthermia in the rabbit was indeed psychotomimetic involved neuropharmacological and behavioral studies. We have developed a semiquantitative method for assessing the potency of psychotomimetic drugs based on their ability to mimic LSD, mescaline, and DOM in producing hypersynchronous (large amplitude, low frequency) or intermittent hypersynchronous activity in the cat EEG.[23] Nonpsychotomimetic phenylalkylamines, such as amphetamine,[24] produce desynchronized (low amplitude, high frequency) activity in this test as well as a greater degree of mydriasis at the dose required to produce effects on the EEG (Figure 3). Previous work in our laboratories[25] had demonstrated a good correlation between psychotomimetic activity in man, ability to produce hyperthermia in rabbits, and activity in modifying rat behavior in the open field. Moreover, the latter test clearly differentiated between psychotomimetic and amphetamine-like aralkylamines. The conjoint use of these three tests—hyperthermia in rabbits, EEG changes in cats, and behavioral responses in rats—has permitted a reliable quantitative analysis to be made of SAR in the phenylalkylamine series.

Results and Discussion

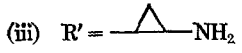
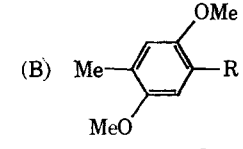
Tables I and II demonstrate that no one compound has a particular type of activity to the exclusion of others; a variety of effects is always present, with either psycho-

Table I. Production of Hyperthermia in Rabbits by Phenylalkylamines

Compd no.	R	Dose, μmol/kg (mg/kg)	Approx time to peak effect, min	Mean max temp rise, °C ± S.E. (method A)	Integrated temp, °C, 0–240 min ± S.E. (method B)	Approx dose for 1° rise, μmol/kg	Potency rel to DOM (95% confidence limits)	
							Method A	Method B
				(A)  R′, (i) R′ = $CH_2CH(Me)NH_2$				
1	2,5-$(OMe)_2$-4-Me	1.0 (0.25)	140	1.93 ± 0.18	330 ± 26			
(DOM)		0.5	120	1.43 ± 0.16	271 ± 31	0.2	1.00	1.00
		0.25	120	1.13 ± 0.09	181 ± 25			
2	2,4,5-$(OMe)_3$	7.6 (2.0)	120	1.88 ± 0.22	325 ± 40			
		3.8	120	1.08 ± 0.16	193 ± 22	2.0	0.10 (0.068–0.155)	0.092 (0.065–0.146)
		1.9	120	0.72 ± 0.16	101 ± 26			
3	2,5-$(OMe)_2$	17.2 (4.0)	80	1.49 ± 0.16	189 ± 28			
		8.6	100	0.97 ± 0.11	105 ± 15	6.6	0.03 (0.019–0.044)	0.025 (0.002–0.070)
		4.3	60	0.46 ± 0.14	53 ± 19			
4	3,4,5-$(OMe)_3$	19.0 (5.0)	100	1.67 ± 0.32	313 ± 36			
		9.5	60	1.13 ± 0.13	144 ± 32	5.5	0.036 (0.02–0.054)	0.03 (0.013–0.015)
		4.75	80	0.55 ± 0.04	75 ± 11			
5	2,5-$(OMe)_2$-4-Cl	0.24 (0.062)	100	2.12 ± 0.35	391 ± 65			
		0.12	80	1.40 ± 0.09	250 ± 20	0.053	3.77 (2.43–5.66)	3.91 (2.56–5.82)
		0.06	80	0.76 ± 0.14	118 ± 32			
6	2,5-$(OMe)_2$-4-Br	0.2 (0.062)	120	1.80 ± 0.22	320 ± 31			
		0.1	100	1.45 ± 0.28	240 ± 41	0.049	4.05 (2.13–6.43)	3.01 (1.11–5.52)
		0.05	100	0.85 ± 0.23	123 ± 41			
7	2,5-$(OMe)_2$-4-Et	0.24 (0.062)	100	1.68 ± 0.17	317 ± 53			
		0.12	80	1.22 ± 0.16	175 ± 30	0.87	2.29 (1.22–3.6)	2.22 (1.20–3.44)
		0.06	60	0.38 ± 0.05	35 ± 19			
8	2,5-$(OMe)_2$-4-*n*-Pr	0.46 (0.125)	100	2.14 ± 0.31	417 ± 65			
		0.23	100	1.31 ± 0.09	265 ± 18	0.84	2.37 (1.34–4.34)	2.44 (0.79–5.67)
		0.115	80	1.20 ± 0.08	214 ± 17			
9	2,5-$(OMe)_2$-4-*i*-Pr	1.84 (0.5)	120	1.06 ± 0.19	200 ± 37			
		0.92	100	0.83 ± 0.26	140 ± 40	1.25	0.16 (0.034–0.324)	0.08 (0.002–0.26)
		0.46	60	0.64 ± 0.09	94 ± 7			
10	2,5-$(OMe)_2$-4-*t*-Bu	6.8 (2.0)	100	2.21 ± 0.93	392 ± 68			
		3.4	100	1.76 ± 0.39	307 ± 82	1.41	0.142 (0.083–0.24)	0.13 (0.044–0.2)
		1.7	80	0.55 ± 0.08	95 ± 19			
11	3-OMe-4-Me	4.6 (1.0)	80	1.06 ± 0.11	160 ± 24	4.0	0.052 (0.016–0.092)	0.019 (0.016–0.068)
		2.3	80	0.75 ± 0.06	127 ± 19			
12	2-OMe-4-Me	9.2 (2.0)	120	1.91 ± 0.25	318 ± 24	2.6	0.078 (0.038–0.158)	0.051 (0.0024–0.186)
		4.6	100	0.90 ± 0.19	140 ± 46			
13	3-OMe-4-Cl	8.4 (2.0)	120	1.13 ± 0.25	189 ± 20	6.5	0.031 (0.0076–0.063)	0.012 (0.005–0.045)
		4.2	120	0.71 ± 0.18	83 ± 29			
14	2-OMe-4-Cl	4.2 (1.0)	120	1.65 ± 0.26	254 ± 22			
		2.1	60	1.57 ± 0.26	218 ± 19	1.21	0.165 (0.006–0.276)	0.078 (0.006–0.18)
		1.05	80	0.57 ± 0.11	85 ± 19			
15	2,4,5-Cl_3	28.8 (8.0)	120	25% died				
		7.2	60	0.86 ± 0.21	126 ± 25	33.3	0.006 (0.0002–0.0205)	0.002 (10^{-11}–0.015)
		1.8	180	0.40 ± 0.07	57 ± 19			
16	2,4-Cl_2	32.8 (8.0)	80	75% died				

		16.4		1.41 ± 0.61	170 ± 83	6.0	0.033 (0.009–0.07)	
		4.1		0.66 ± 0.33	113 ± 40			
17	4-Me	27 (5.0)		All died				
		10.8	60	0.95 ± 0.06	111 ± 42	>10.8 < 27		
18	4-Cl	24 (5.0)		All died				
		9.6	40	0.92 ± 0.22	111 ± 39	>9.0 < 24		
19	4-Br	20 (5.0)		All died				
		8	60	0.6 ± 0.17	80 ± 34	>8.0 < 20		
20	H	27.2 (10)	40	2.03 ± 0.41	232 ± 52	>13 < 27		
(amphetamine)		13.6	60	0.66 ± 0.21	102 ± 30			
LSD		0.026 (0.012)	80	1.7 ± 0.12	310 ± 35			
		0.013	80	1.35 ± 0.11	232 ± 35	0.0061	33 (21.5–54)	31.7 (21.7–47.8)
		0.0062	80	1.07 ± 0.06	134 ± 31			
Mescaline		344 (80)	80	1.0 ± 0.35	120 ± 30			
		172	40	0.5 ± 0.1	36 ± 12	344	~0.0006	
1, *R*-(−)		0.5 (0.125)	100	1.81 ± 0.25	286 ± 38			
		0.25	80	1.43 ± 0.22	253 ± 54	0.11	1.8 (0.93–3.04)	1.7 (0.72–3.1)
		0.125	40	1.06 ± 0.15	188 ± 32			
1, *S*-(+)		4.0 (1.00)	100	1.71 ± 0.12	317 ± 32			
		2.0	100	1.24 ± 0.13	196 ± 35	1.13	0.177 (0.092–0.29)	0.16 (0.008–0.265)
		1.0	100	0.97 ± 0.16	122 ± 45			
2, *R*-(−)		3.9 (1.00)	100	1.58 ± 0.21	277 ± 43			
		1.95	100	1.40 ± 0.18	240 ± 35	0.95	0.209 (0.116–0.334)	0.17 (0.062–0.33)
		0.95	100	0.75 ± 0.17	111 ± 33			
2, *S*-(+)		30.4 (8.0)	80	1.29 ± 0.08	209 ± 17			
		15.2	60	1.01 ± 0.14	177 ± 22	16.5	0.013 (0.004–0.021)	0.01 (0.002–0.021)
		7.6	80	0.72 ± 0.18	104 ± 24			
3, *R*-(−)		8.6 (2.0)	60	1.45 ± 0.27	179 ± 34			
		4.3	60	1.23 ± 0.17	140 ± 31	2.9	0.07 (0.03–0.11)	0.025 (0.002–0.07)
		2.15	40	0.55 ± 0.13	74 ± 31			
3, *S*-(+)		43.0 (10.0)	60	1.72 ± 0.22	247 ± 43			
		21.5	60	1.04 ± 0.17	130 ± 34	13.3	0.015 (0.01–0.022)	0.009 (0.003–0.015)
		10.75	80	0.46 ± 0.09	38 ± 12			
4, *R*-(−)		9.5 (2.5)	100	1.58 ± 0.15	263 ± 35			
		4.75	80	1.09 ± 0.15	159 ± 20	3.2	0.062 (0.041–0.085)	0.045 (0.022–0.074)
		2.37	80	0.39 ± 0.08	43 ± 8			
4, *S*-(+)		76 (20)	160	1.57 ± 0.44	272 ± 89			
		38	120	0.89 ± 0.21	197 ± 37	27.4	0.007 (0.003–0.011)	0.006 (0.001–0.01)
		19	100	0.41 ± 0.08	40 ± 9			
5, *R*-(−)		0.24 (0.062)	80	2.53 ± 0.39	460 ± 58			
		0.12	100	1.38 ± 0.113	235 ± 23	0.046	4.36 (3.08–6.06)	3.59 (2.28–5.23)
		0.06	80	0.91 ± 0.09	131 ± 18			
5, *S*-(+)		1.92 (0.5)	100	2.1 ± 0.25	358 ± 44			
		0.96	70	1.5 ± 0.29	205 ± 71	0.50	0.45 (0.27–0.73)	0.28 (0.08–0.58)
		0.48	80	0.6 ± 0.12	80 ± 8			
6, *R*-(−)		0.1 (0.031)	140	1.98 ± 0.35	341 ± 59			
		0.05	100	0.98 ± 0.10	152 ± 21	0.029	6.93 (3.88–11.02)	4.93 (1.31–9.53)
		0.025	100	0.80 ± 0.15	134 ± 31			
6, *S*-(+)		0.8 (0.25)	120	1.33 ± 0.23	224 ± 46			
		0.4	120	0.96 ± 0.26	150 ± 51	0.42	0.49 (0.166–0.85)	0.25 (0.006–0.655)
		0.2	120	0.56 ± 0.14	66 ± 24			
				(ii) R′ = $(CH_2)_2CH(Me)NH_2$				
21	3,4-$(OMe)_2$	163 (40)		Lethal				
		20.4		Negative				

Table I (*continued*)

Compd no.	R	Dose, μmol/kg (mg/kg)	Approx time to peak effect, min	Mean max temp rise, °C ± S.E. (method A)	Integrated temp, °C, 0–240 min ± S.E. (method B)	Approx dose for 1° rise, μmol/kg	Potency rel to DOM (95% confidence limits)	
							Method A	Method B
22	3,4-OCH_2O	174 (40)		Lethal				
		21.7		Negative				
23	2,4,5-$(OMe)_3$	144 (40)	180	0.9 ± 0.3	118 ± 30			
		36	220	0.4 ± 0.2	62 ± 22	~190	~0.001	
		18	120	0.26 ± 0.12	42 ± 14			
24	2,4,6-$(OMe)_3$	144 (40)		Lethal				
		18		Negative				
25	2,3,4-$(OMe)_3$	144 (40)		Lethal				
		18		Negative				
26	2,5-$(OMe)_2$-4-Me	38.4 (10)	120	2.1 ± 0.81	316 ± 47	~20	~0.01	
		19.2	100	0.6 ± 0.41	102 ± 17			
				(iii) R' = 				
27	2,4,5-$(OMe)_3$ (trans)	1.92 (0.5)	60	1.80 (25% died)	213 (25% died)	~1.0	~0.2	
		0.96	60	0.87 ± 0.23	90 ± 15			
28	2,5-$(OMe)_2$-4-Me (trans)	1.02 (0.25)	60	1.35 (25% died)	217 (25% died)	~0.5	~0.35	
		0.51	60	1.05 ± 0.11	111 ± 19			
29	4-Cl (trans)	24.4 (5.0)	40	0.72 ± 0.08	105 ± 21	>24	<0.01	
		9.8		Negative				
30	4-Cl (cis)	24.3 (5.0)	80	0.43 ± 0.11	67 ± 21	>24	<0.01	
		9.8		Negative				
31	4-Br (trans)	20 (5.0)	60	0.69 ± 0.13	98 ± 25	>20	<0.01	
		8.0		Negative				
32	4-Br (cis)	20 (5.0)	60	0.4 ± 0.4	57 ± 6	>20	<0.01	
		8.0		Negative				
				(B) 				
33	$CH(Me)CH_2NH_2$	16 (4)	100	1.48 ± 0.34	252 ± 73	7.4	0.027 (0.01–0.049)	0.016 (0.001–0.039)
		4	40	0.47 ± 0.12	53 ± 13			
34	$C(Me)_2CH_2NH_2$	30 (8)	100	0.34 ± 0.08	54 ± 17			
		15		Negative	Negative			
35	$CH(Me)CH(Me)NH_2$	4 (1)	100	1.17 ± 0.15	203 ± 28	2.6	0.076 (0.022–0.139)	0.039 (0.024–0.107)
		2	60	0.95 ± 0.22	123 ± 46			
36	$CH_2CH(Me)NHMe$	7.5 (2)	100	1.20 ± 0.15	205 ± 24			
		3.75	80	0.70 ± 0.20	115 ± 19	5.5	0.036 (0.011–0.067)	0.019 (0.006–0.057)
		1.87	60	0.44 ± 0.22	69 ± 20			
37	$CH_2CH(Me)NHEt$	14.4 (4)	80	1.81 ± 0.52	341 ± 94			
		7.2	80	0.94 ± 0.17	123 ± 33	5.0	0.04 (0.016–0.07)	0.027 (0.004–0.061)
		3.6	80	0.65 ± 0.23	90 ± 33			

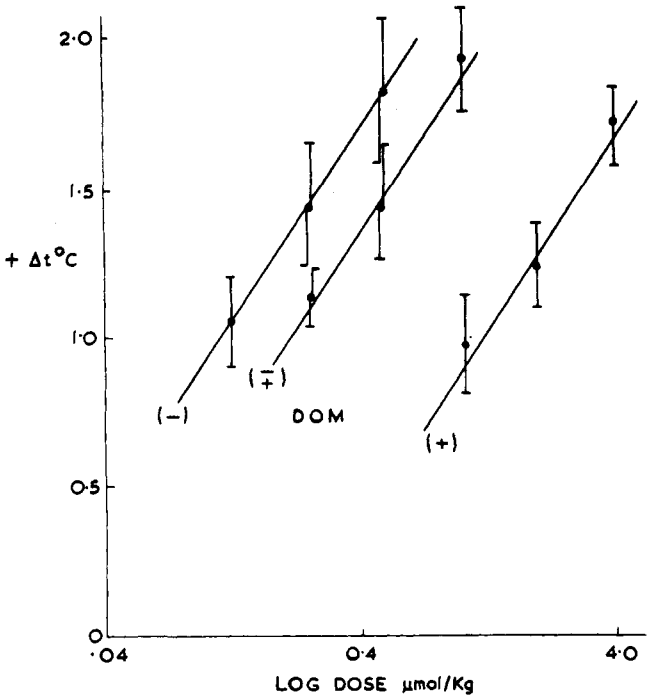


Figure 2. Induced hyperthermia in rabbits. Dose–response lines obtained for enantiomers and racemate of DOM (bars indicate standard errors of mean).

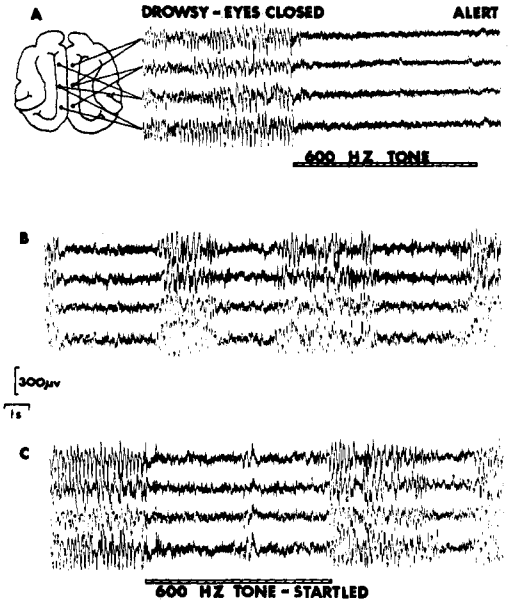


Figure 3. Effect of DOM on EEG of cat carrying permanently implanted electrodes: A, normal cat aroused by a 600-Hz tone stimulus; B, 15 min after 125 μg/kg (im) of DOM; cat still, alert, and eyes fixed on object in recording chamber; C, 15 min after 250 μg/kg (im) of DOM; "phasic" EEG response—cat startled by 600-Hz tone stimulus with immediate return of 4–6-Hz activity in EEG after termination of 600-Hz tone.

tomimetic or psychostimulant activity predominating depending upon the structure of the particular compound. Our differentiation between the various biological actions of the phenylisopropylamines is in direct contrast to many other pharmacological studies, such methods as disruption of CAR or other behavioral responses[3-5,7,22] doing little more than indicate a generalized central stimulation. Our approach is justified by the close correlation between the measures of relative potency in producing hyperthermia in the rabbit and psychotomimetic potencies reported for man (Table III). This correlation is particularly close when it is realized that there are probably great differences between man and experimental animals in factors such as drug transport, absorption, and metabolism.

The results possibly allow the methods to be extrapolated to the human situation once a standard compound is available, common to both animal and human studies. Such a compound is DOM, which has been tested in both situations; it is arbitrarily assigned a potency of 1.0 in the hyperthermia test, and our analysis of SAR in the phenylalkylamine series is based upon this test and on DOM as the reference compound.

The major point to emerge from the results is that a 4-substituent in the aromatic ring is essential for high psychotomimetic activity. Thus, compounds **17–19**, though still mainly amphetamine-like in their effects on the EEG and pupil diameter, exhibit a higher degree of LSD-like activity in their pharmacological spectrum than does amphetamine itself (**20**). Furthermore, 2,5-dimethoxyphenylisopropylamine (**3**) is less potent in producing hyperthermia and more amphetamine-like in its effects on cat EEG and rat behavior in the open field than other compounds (**1**, **2**, **5–10**) which also carry a 4-substituent in addition to retaining this pattern. The potentiation of effects shown by this structure may reflect the known susceptibility of phenylisopropylamines to 4-hydroxylation as their principal route of metabolism in lower species.[26] However, aromatic hydroxylation is a relatively minor route in higher species including man and it would be unwise to extrapolate our results without further experimentation. There appears to be a steric restriction on the 4-substituent—activity in the 2,5-dimethoxy-4-alkylphenylisopropylamines is in the order *n*-Pr (**8**) > Et (**7**) > Me (**1**) > *i*-Pr (**9**) > *t*-Bu (**10**)—while there is only a very slight increase in potency in going from 4-Cl (**5**) to 4-Br (**6**). This trend is confirmed by results obtained from stimulation of smooth muscle preparations *in vitro*[8] and from production of scratching responses in mice,[22] though the latter study suggested that the isopropyl compound **9** was the most potent. Nevertheless, our results confirm the suggestions[2,8] that halo or alkyl substitution in the 4 position is associated with a higher degree of psychotomimetic activity than substitution by the typical methoxyl group.

2,5-Dimethoxy substitution is clearly associated with high activity in our series, with the 2-methoxy being somewhat more important. Thus, the hyperthermia data indicate that **2** is more potent than **4**, **12** > **11**, and **14** > **13**, though the other pharmacological studies show that the latter four compounds possess both amphetamine-like and LSD-like effects to almost equal degrees in their pharmacological spectra. It is significant that while replacement of a 4-methoxy group by halogen enhances psychotomimetic activity, with enhanced LSD-like effects on rectal temperature and cat EEG and **5** and **6** being more potent than **2**, a marked deleterious effect is observed when the 2- or 5-methoxy groups are replaced. Thus, both 2,4-dichloro- (**16**) and 2,4,5-trichlorophenylisopropylamine (**15**) are virtually devoid of LSD-like properties in all three test systems but do have pronounced amphetamine-like activity.

Modifications to the isopropylamine side chain had a generalized deleterious effect on psychotomimetic activity. Our results confirm and extend previous studies which were limited to replacing the α-methyl group of various amphetamines by alkyl,[27] trifluoromethyl,[28] or cyano[29] groups. In the 3-amino-1-phenylbutane series, only two compounds (**23** and **26**) produced a significant degree of hyperthermia in rabbits and only the latter resembled LSD in its effects in the open field, though both compounds produced hypersynchronous activity in the cat

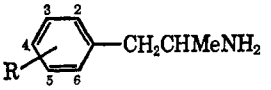
Table II. Results of Neuropharmacological and Behavioral Studies of Phenylalkylamines

Compd no.	Open field		Cats carrying permanently implanted electrodes	
	Compds producing LSD-like effects; lowest dose producing effect in μmol/kg (mg/kg)	Compds not showing LSD-like effects; lowest dose producing effect and effect seen[a]	Dose required (μmol/kg im) to produce phasic electrocortical response between 4 and 6 Hz activity (hypersynchronous)	Deg of mydriasis produced at the dose required for electrocortical arousal[b]
1	0.44 (0.01)		>1 < 2	+
2	3.82 (1.00)		>10 < 20	+
3		21.59 (5.00) D ↓	>21.5 < 43	+
4		7.65 (2.00) D ↓, SQ ↓	>19 < 38	+
5	0.75 (0.20)		>0.24 < 0.48	+
6	0.064 (0.02)		>0.2 < 0.4	+
7	0.38 (0.10)		>0.24 < 0.48	+
8	0.073 (0.02)		>0.23 < 0.46	+
9	1.83 (0.5)			
10	6.96 (2.00)			
11		No effects	>9 < 18	++
12	23.20 (5.00)		>18 < 36	++
13	21.19 (5.00)		>8.4 < 16.8	++
14		4.24 (1.0) R ↑, SQ ↑, CSQ ↑	>8.4 < 16.8	+
15		No effects	4–6 Hz burst activity at 1.8, no phasic arousal at 18.8	++ at 18.8
16	2.05 (0.5)			
17	10.78 (2.00)		4–6 Hz burst activity at 5.4, desynchronization at 43.2	+++ at 43.2
18	4.85 (1.00)		>9.6 < 19.2	++++
19	2.00 (0.50)		>8 < 16	++++
20		2.17 (0.50) R ↑, SQ ↑, CSQ ↑	Desynchronization at 27	++++
LSD	0.11 (0.05)		>0.05 < 0.1	+
Mescaline	19.12 (5.00)		>43 < 315	++
21		40.73 (10.00) CSQ ↓		
22		No effects		
23		39.44 (10.00) SQ ↑	>72 < 144	+
24		36.29 (10.00) D ↓		
25		No effects		
26	20.53 (5.00)		>19 < 38	+
27	3.85 (1.00)		>1.9 < 3.8	+
28	0.41 (0.10)		>1.02 < 2.04	+
29	2.45 (0.50)			
30	0.49 (0.10)			
31	2.01 (0.50)			
32	4.02 (1.00)			
33		No effects	Desynchronization at 80	+++ at 80
34		No effects		
35		2.00 P ↑		
36		No effects	4–6 Hz burst activity at 30, desynchronization at 60	++ at 60
37		No effects		
1, *R*-(−)	0.44 (0.10)		>0.5 < 0.1	+
1, *S*-(+)	40.73 (10.00)		>10 < 20	+
2, *R*-(−)	0.76 (0.2)		>4.9 < 19.5	+
2, *S*-(+)		19.10 (5.0) P ↑, CSQ ↑	>49 < 98	+
3, *R*-(−)		8.64 (2.0) D ↓, SQ ↓	>10.7 < 21.5	+
3, *S*-(+)		43.18 (10.0) SQ ↑	>215	+
4, *R*-(−)	7.65 (2.0)		>9.5 < 19	+
4, *S*-(+)		38.25 (10.0) D ↓	>47.5 < 95	+
5, *R*-(−)	0.38 (0.10)		>0.24 < 0.48	+
5, *S*-(+)	1.61		>0.57 < 1.14	+
6, *R*-(−)	0.03		>0.03 < 0.20	+
6, *S*-(+)	0.64 (0.20)		>1.0 < 2.0	+

[a] ↑ = increase; ↓ = decrease; SQ = squares traversed; CSQ = central square; R = rearing; D = defecation; P = preening. [b] +, pupil less than 25% dilated; ++, pupil 25–50% dilated; +++, pupil 50–75% dilated; ++++, pupil 75% to maximal dilation.

EEG. These results again emphasize the importance of a 2,4,5-trisubstitution pattern, particularly of the type present in DOM. When the α-methyl group is moved to the β position (**33**), or two methyl groups are present (**34** and **35**), the resulting compounds have virtually no psychotomimetic activity although they do cause hyperthermia at high doses. N-Alkylation, by either methyl (**36**) or ethyl (**37**), also resulted in a pronounced decrease in LSD-like activity in all three test systems and a corresponding enhancement of amphetamine-like properties. This is in agreement with the work of Ho's group,[30] but in contrast to the compounds reported by Knoll[20] who described the appearance of psychotomimetic activity following N-methylation of various phenylisopropylamines; the dis-

Table III. Comparative Potency of Some Phenylisopropylamines in Producing a Mescaline-Like Syndrome in Man and a Rise in Rectal Temperature in Rabbits



R	Man[a]	Rabbit[b]
Mescaline	1.0[c]	0.08
2,5-(OMe)$_2$	8[c]	3.6
3,4,5-(OMe)$_3$	2.2[c]	4.4
2,4,5-(OMe)$_3$	17[c]	12.1
(±)-2,5-(OMe)$_2$-4-Me	80[c]	120
(−)-2,5-(OMe)$_2$-4-Me	160[d]	216
(+)-2,5-(OMe)$_2$-4-Me	<40[d]	21.4
2,5-(OMe)$_2$-4-Et	150[e]	277
2,5-(OMe)$_2$-4-Br	400[f]	491
LSD	4000[g]	4000

[a] With mescaline as standard. The potency of each compound is expressed in mescaline units, defined as the quotient of the effective dose of mescaline divided by the effective dose of the compound, both calculated as the free base. The effective dose was taken as the mean of the threshold dose, where psychotomimetic effects were just apparent, and the dosage that was maximally effective. The effective dose for mescaline in man is 3.75 mg/kg. [b] With LSD as standard (mescaline is relatively poor compared to the phenylisopropylamines in raising rabbit rectal temperature). [c] A. T. Shulgin, T. Sargent, and C. Naranjo, *Nature (London)*, **221**, 537 (1969). [d] A. T. Shulgin, *J. Pharm. Pharmacol.*, **25**, 271 (1973). [e] S. H. Snyder, L. A. Faillace, and R. H. Weingartner, *Arch. Gen. Psychiat.*, **21**, 95 (1969). [f] A. T. Shulgin, T. Sargent, and C. Naranjo, *Pharmacology*, **5**, 103 (1971). [g] S. Cohen, *Progr. Drug. Res.*, **15**, 68 (1971).

crepancy could be due to the different test procedures, Knoll's behavioral studies in cats and rodents being possibly less predictive of psychotomimetic activity.

Incorporation of the α-methyl group into a cyclopropane ring had less effect upon psychotomimetic activity than other side-chain modifications, and the compounds (**27**-**32**) retained much of the activity of the parent amphetamines. 2-(2,5-Dimethoxy-4-methylphenyl)cyclopropylamine (**28**) produced the full LSD-like response and is about one-third as potent as DOM, while the 2,4,5-trimethoxy analog **27** is more active in producing hyperthermia than the corresponding amphetamine **2** though **27** and **2** are almost equipotent in the open-field test. It is significant that the 4-bromo and 4-chloro compounds **31** and **29**, although they are of relatively low potency, also showed the full LSD-like response, while the corresponding amphetamines had a greater degree of amphetamine-like activity in their pharmacological spectrum. These results are in accord with those reported for 2-(3,4,5-trimethoxyphenyl)cyclopropylamine[31,32] and also confirm, albeit tentatively, that the trans isomers **29** and **31** are somewhat more potent in producing hyperthermia than are the cis **30** and **32**, though the reverse is true in the open-field studies.

Psychotomimetic activity in the phenylisopropylamines, as measured in this study by hyperthermia and confirmed by behavioral and neuropharmacological studies, clearly resides in the *R*-(−) enantiomers which are in general about twice as potent as the racemates and up to 12.6 times as potent as the *S*- (+) enantiomers (Table IV). Our results extend and confirm those reported for DOM in man,[6] for DOM and **6** in CAR in rats,[7] and for a series of phenylisopropylamines as stimulants of smooth muscle.[8] While this difference in activity between enantiomers undoubtedly reflects differences in drug-receptor interaction, the quantitative validity of the results is in question. This illustrates the main problem in assessing SAR in the CNS of whole animals: the quantitative nature of the results depends not only on drug-receptor interactions but also on such factors as extent and rate of metabolism, distribution, and transport. Nevertheless, the relative inactivity of the *S*-(+) enantiomers supports the contention[6-8] that a selective, asymmetric site is associated with the mechanism of action of psychotomimetic phenylisopropylamines. That this site is also common to LSD is indicated by the close stereochemical relationship between the (*R*)-(−)-phenylisopropylamines and the psychotomimetically active isomer of LSD (5*R*:8*R*).[12]

Table IV. Induced Hyperthermia in Rabbits. Enantiomeric Potency Ratios

Compd no.	Ratio *R*-(−):*S*-(+) (95% confidence limits)	
	Method A	Method B
1	10.2 (5.4-20.0)	11.2 (5.4-28.0)
2	12.6 (8.9-18.5)	12.6 (9.7-16.9)
3	5.0 (3.2-7.8)	4.7 (2.7-7.9)
4	8.5 (6.0-12.5)	8.4 (6.7-10.4)
5	9.4 (6.7-13.2)	10.28 (7.66-13.98)
6	12.2 (7.7-27.8)	12.8 (7.7-27.8)

In conclusion, it can be stated that optimum activity in psychotomimetic phenylisopropylamines is associated with (a) an isopropylamine side chain with a *R*-(−) configuration at the carbon atom α to the primary amino group, and (b) 2,5-dimethoxy substitution together with an alkyl or halo group at position 4 that is probably limited in bulk to *n*-propyl or bromo.

Experimental Section

Chemistry. All melting points are uncorrected and were determined in an Electrothermal capillary apparatus. New compounds were identified by ir, uv, and nmr spectroscopy, and satisfactory analyses (±0.4% of calculated values) are indicated by elemental symbols.

(A) Phenylisopropylamines. 4-Alkyl-2,5-dimethoxybenzaldehydes were prepared by Vilsmeier-Haack formylation of the appropriate hydrocarbon, using $POCl_3$-*N*-methylformanilide under standard conditions.[33] Data [alkyl, yield (%), bp or mp (°C), analyses]: Et, 50, 125° (0.2 mm), C, H, N (as the 2,4-dinitrophenylhydrazone, mp 248°); *n*-Pr, 55, 135° (0.2 mm), C, H, N (as the 2,4-dinitrophenylhydrazone, mp 220°); *i*-Pr, 30, 70°, C, H; *t*-Bu, 35, 125°, C, H.

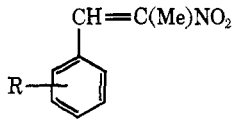
4-Chloro-2-methoxy- and 3-methoxy-4-methylbenzaldehyde were prepared by sulfoxide oxidation[34] of the corresponding benzyl alcohols. 3-Methoxy-4-methylbenzaldehyde, obtained in 80% yield, was characterized as its 2,4-dinitrophenylhydrazone, mp 241°. *Anal.* C, H, N. 2-Methoxy-4-chlorobenzaldehyde, yield 35%, mp 69-70° (C_6H_6), was also characterized as its 2,4-dinitrophenylhydrazone, mp 237-238°. *Anal.* C, H, N.

2,4,5-Trichlorobenzaldehyde. 2,4-Dichlorobenzaldehyde (17.5 g, 0.1 mol) in concentrated H_2SO_4 (300 ml) was treated at 0° with a solution of KNO_3 (10.1 g, 0.1 mol) in concentrated H_2SO_4 (50 ml), and the mixture was stirred at 0° for 1.5 hr. It was then poured with stirring into cold H_2O (1.5 l.), and the precipitated oil, which rapidly solidified, was collected, washed (H_2O), and dried before recrystallizing from isopropyl ether. 2,4-Dichloro-5-nitrobenzaldehyde had mp 55-57°, yield 55%. *Anal.* C, H, N.

This compound (8.5 g) was added to a solution of $SnCl_2 \cdot 2H_2O$ (28 g) in concentrated HCl (30 ml) at 0° and the slurry was stirred for 1 hr. The reduction was strongly exothermic, the temperature rising to 90°. The reaction mixture was diluted with H_2O (50 ml) and treated at 0° with a solution of $NaNO_2$ (3 g) in H_2O (20 ml). The diazonium salt solution was poured into a solution of CuCl (25 g) in concentrated HCl (50 ml), and the product was isolated by steam distillation. Recrystallization from *i*-Pr_2O gave 2,4,5-trichlorobenzaldehyde, mp 110°, yield 62%. *Anal.* C, H.

β-Methyl-β-nitrostyrenes (Table V) were obtained by Knoevenagel condensation of the appropriate benzaldehyde, by heating under reflux for 3 hr with a three-fold excess of $EtNO_2$ in glacial AcOH containing NH_4OAc.[5] 4-Chloro-2-methoxy-β-methyl-

Table V



R	Mp, °C	Yield, %	Formula[a]
3-OMe-4-Me	47–48	49	$C_{11}H_{13}NO_3$
3-OMe-4-Cl	68–70	48	$C_{10}H_{10}ClNO_3$
4-Br	85–86	60	$C_9H_8BrNO_2$
2,5-$(OMe)_2$-4-Et	63–64	85	$C_{13}H_{17}NO_4$
2,5-$(OMe)_2$-4-*n*-Pr	96–97	86	$C_{14}H_{19}NO_4$
2,5-$(OMe)_2$-4-*i*-Pr	77–78	85	$C_{14}H_{19}NO_4$
2,5-$(OMe)_2$-4-*t*-Bu	100–101	70	$C_{15}H_{21}NO_4$
2,4-Cl_2	79–81	76	$C_9H_7Cl_2NO_2$
2,4,5-Cl_3	69–70	70	$C_9H_6Cl_3NO_2$

[a] All compounds were analyzed for C, H, and N.

β-nitrostyrene was not obtained pure and was used directly for the next stage.

Phenylisopropylamines (Table VI) were typically prepared by $LiAlH_4$ reduction in THF of the corresponding β-methyl-β-nitrostyrene.

4-Bromo-2,5-dimethoxyphenylisopropylamine Hydrobromide (6). To a solution of 2,5-dimethoxyamphetamine (1.5 g) in glacial AcOH (7.5 ml) was added a 50% solution of HBr in glacial AcOH (1.25 g), and to this mixture at 0–5° was added a solution of Br_2 (1.23 g) in glacial AcOH (10 ml). The reaction mixture was stirred for 3 hr at room temperature and concentrated *in vacuo*, and the residue was recrystallized from EtOAc.

4-Chloro-2,5-dimethoxyphenylisopropylamine Hydrochloride (5). Dry HCl was passed into a solution of 2,5-dimethoxyamphetamine (2.64 g) in glacial AcOH (15 ml) until 0.4 g had been absorbed. To this stirred solution at 0–5° was added a solution of Cl_2 (0.9 g) in glacial AcOH (15 ml), the whole mixture was stirred at room temperature for 5 hr. Concentration *in vacuo* and recrystallization from EtOAc gave impure product, which was purified by further recrystallization from 2-propanol–Et_2O.

(B) 1-Phenyl-3-aminobutanes. 1-Phenylbutan-3-ones. Typically, a mixture of 1,2,4-trimethoxybenzene (5.6 g, 0.033 mol), methyl vinyl ketone (4.6 g, 0.066 mol), and $C_2H_2Cl_4$ (10 ml) was cooled to 0° and treated dropwise with $BF_3 \cdot Et_2O$ (4.7 g, 0.033 mol). The mixture was stirred at room temperature for 3 hr and poured into H_2O, and the organic phase was extracted into Et_2O, washed with water and 2 *N* NaOH, and dried ($MgSO_4$). Fractional distillation gave 4.1 g (53%) of a pale yellow oil, bp 107–110° (0.1 mm), mp 47–48° (*i*-Pr_2O).

1-Phenyl-3-hydroxyiminobutanes. For example, 1-(2,4,5-trimethoxyphenyl)butan-3-one (17.4 g, 0.073 mol) was added to an aqueous solution of NaOAc (12 g) and $NH_2OH \cdot HCl$ (6.75 g). Sufficient EtOH was added to render the solution homogeneous, and it was then heated under reflux for 30 min. EtOH was removed *in vacuo*, H_2O (100 ml) was added, and the organic phase extracted into C_6H_6. Chromatography on a silica gel G column, using C_6H_6–Et_2O (7:3) as eluent, gave pure oxime, mp 76°, yield 11.6 g (63%).

1-Phenyl-3-aminobutanes (Table VII) were obtained from the oximes either by $LiAlH_4$ reduction in Et_2O or by catalytic reduction in ethanolic HCl using PtO_2 as catalyst at room temperature and 2.8 kg cm^{-2}.

(C) 2-Phenylcyclopropylamines were prepared by reaction between ethyl diazoacetate and a styrene followed by Curtius transformation (method A)[9] or by reaction between a cinnamate and dimethylsulfoxonium methylide followed by Curtius transformation (method B).[10] New compounds are listed in Table VIII.

(D) *N*-Alkylamphetamines. 2,5-Dimethoxy-4,*N*-dimethylphenylisopropylamine hydrochloride (36) was prepared from DOM by successive reaction with benzaldehyde and Me_2SO_4.[30]

***N*-Acetyl-2,5-dimethoxy-4-methylphenylisopropylamine.** A mixture of DOM (2 g, 11 mmol), AcCl (3 g, 38 mmol), and a few drops of trifluoromethylsulfonic acid was heated under reflux for 6 hr. The cooled mixture was diluted with H_2O and basified with 10% NaOH to give a light brown oil which slowly solidified. Recrystallization from C_6H_{12} gave 1.3 g (60%) of yellow needles, mp 132–133°. *Anal.* C, H, N.

***N*-Ethyl-2,5-dimethoxy-4-methylphenylisopropylamine (37).** The *N*-acetyl derivative was reduced with $LiAlH_4$ in THF to give 82%, mp 171–172° (*i*-PrOH). *Anal.* C, H, N.

(E) Miscellaneous Phenylalkylamines. 2,5-Dimethoxy-α,4-dimethylphenylacetonitrile. A mixture of 2,5-dimethoxy-4-methylphenylacetonitrile (2 g, 10 mmol) and $NaNH_2$ (0.45 g, 13 mmol) in dry C_6H_6 (15 ml) was heated under reflux for 3 hr, until evolution of NH_3 was complete. MeI (1.6 g, 13 mmol) in dry C_6H_6 (25 ml) was then added to the cooled mixture, which was heated under reflux for a further 3 hr. The cooled mixture was poured into cold H_2O; the C_6H_6 layer was separated, dried ($MgSO_4$), and distilled to give 1.5 g (71%) of a colorless oil, bp 140–142° (2.5 mm). *Anal.* C, H, N.

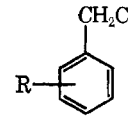
Further alkylation of this nitrile gave **2,5-dimethoxy-α,α,4-trimethylphenylacetonitrile** in 63% yield, bp 100–103° (0.1 mm). *Anal.* C, H, N.

Reduction of the above nitriles with $LiAlH_4$ in THF gave respectively **2-(2,5-dimethoxy-4-methylphenyl)propylamine hydrochloride (33)** [mp 209–210° (EtOH), yield 78%. *Anal.* C, H, N] and **2-(2,5-dimethoxy-4-methylphenyl)-2-methylpropylamine hydrochloride (34)** [mp 140–141°, yield 64%. *Anal.* C, H, N].

2,5-Dimethoxy-4-methylphenylpropanone. A mixture of 2,5-dimethoxy-4-methylnitrostyrene[30] (5 g, 20 mmol), Fe powder (10 g), $HClO_4$ (0.5 ml), and H_2O (200 ml) was heated under reflux with *vigorous* stirring for 6 hr. The cooled mixture was treated with concentrated HCl (100 ml) and again heated under reflux for 1 hr. H_2O (1 l.) was added and the mixture was extracted with Et_2O (3 × 250 ml). The combined ether extracts were dried ($MgSO_4$) and distilled to give 2.2 g (54%) of a pale-yellow oil, bp 115–118° (0.4 mm). *Anal.* C, H.

Alkylation of this propanone with $NaNH_2$–MeI gave a 58%

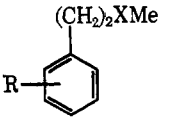
Table VI



R	Mp, °C	Yield, %	Recrystn solvent	Formula[a]
2,5-$(OMe)_2$-4-Cl	187–188[b]	50	Me_2CO–EtOH	$C_{11}H_{16}ClNO_2 \cdot HCl$
2,5-$(OMe)_2$-4-Br[c]	145–146[d]	70	EtOAc	$C_{11}H_{16}BrNO_2 \cdot HBr$
2,5-$(OMe)_2$-4-Et	188–190	54	EtOH–Et_2O	$C_{13}H_{21}NO_2 \cdot HCl$
2,5-$(OMe)_2$-4-*n*-Pr	283–284	60	EtOH–Et_2O	$C_{14}H_{23}NO_2 \cdot HCl$
2,5-$(OMe)_2$-4-*i*-Pr	183–184	58	EtOH–Me_2CO	$C_{14}H_{23}NO_2 \cdot HCl$
2,5-$(OMe)_2$-4-*t*-Bu	164–166	60	EtOH–Me_2CO	$C_{15}H_{23}NO_2 \cdot HCl$
2-OMe-4-Me	112–114[e]	56	EtOAc	$C_{11}H_{16}NO \cdot HCl$
3-OMe-4-Me	159–160[f]	48	Me_2CO	$C_{11}H_{16}NO \cdot HCl$
2-OMe-4-Cl	147–149	41	EtOH–EtOAc	$C_{10}H_{14}ClNO \cdot HCl$
3-OMe-4-Cl	137–138	53	Me_2CO–EtOAc	$C_{10}H_{14}ClNO \cdot HCl$
2,4,5-Cl_3	195–196	60	EtOH–Et_2O	$C_9H_{10}Cl_3N \cdot HCl$
2,4-Cl_2	194–195	55	EtOH–Et_2O	$C_9H_{11}Cl_2N \cdot HCl$

[a] All compounds were analyzed for C, H, and N. [b] R. T. Coutts and J. L. Malicky, *Can. J. Chem.*, **51**, 1402 (1973), reported mp 193–194.5°. [c] Analyzed as the HBr salt. [d] Coutts and Malicky give mp 195–196° for the hydrochloride. [e] R. Baltzly and J. S. Buch, *J. Amer. Chem. Soc.*, **62**, 161 (1940), reported mp 117.5°. [f] Lit.[5] mp 182–183°.

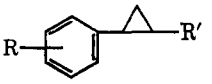
Table VII



R	X	Mp or bp (mm), °C	% yield	Recrystn solvent	Formula[c]
2,3,4-(OMe)$_3$	CO	118–120 (0.1)	40		$C_{13}H_{18}O_4$
2,4,5-(OMe)$_3$	CO	47–48	53	*i*-Pr_2O	$C_{13}H_{18}O_4$
2,4,6-(OMe)$_3$	CO	140–142 (0.1)	45		$C_{13}H_{18}O_4$
2,5-(OMe)$_2$-4-Me	CO	106–108 (0.2)	60		$C_{13}H_{18}O_3$
3,4-(OMe)$_2$	C(=NOH)[a]	88–89	61	C_6H_{12}	$C_{12}H_{17}NO_3$
3,4-OCH$_2$O	C(=NOH)[a]	86–88	55	C_6H_{12}	$C_{11}H_{13}NO_3$
2,3,4-(OMe)$_3$	C(=NOH)	83–84	72	*i*-Pr_2O	$C_{13}H_{19}NO_4$
2,4,5-(OMe)$_3$	C(=NOH)	76–77	63	C_6H_{12}	$C_{13}H_{19}NO_4$
2,4,6-(OMe)$_3$	C(=NOH)	89–90	65	*i*-Pr_2O	$C_{13}H_{19}NO_4$
2,5-(OMe)$_2$-4-Me	C(=NOH)	84–85	75	MeOH	$C_{13}H_{19}NO_3$
3,4-(OMe)$_2$	CH(NH$_2$)[b]	150–151	74	Me_2CO–MeOH	$C_{12}H_{19}NO_2 \cdot HCl$
3,4-OCH$_2$O	CH(NH$_2$)[b]	122–123	27	Me_2CO–MeOH	$C_{11}H_{15}NO_2 \cdot HCl$
2,3,4-(OMe)$_3$	CH(NH$_2$)	152–153	60	EtOH	$C_{13}H_{21}NO_3 \cdot HCl$
2,4,5-(OMe)$_3$	CH(NH$_2$)	176	40	Me_2CO–EtOH	$C_{13}H_{21}NO_3 \cdot HCl$
2,4,6-(OMe)$_3$	CH(NH$_2$)	183–184	52	Me_2CO–EtOH	$C_{13}H_{21}NO_3 \cdot HCl$
2,5-(OMe)$_2$-4-Me	CH(NH$_2$)	215–217	65	EtOH	$C_{13}H_{21}NO_2 \cdot HCl$

[a]These compounds were prepared by reduction of the benzylideneacetones. [b]These compounds were prepared by catalytic reduction. [c]All compounds were analyzed for C, H, or C, H, and N.

Table VIII



R	R′	Configuration	Method	% yield	Mp or bp (mm), °C	Formula[a]
4-Br	CO_2Et	Trans	B	75	148–149 (2.0)	$C_{12}H_{13}BrO_2$
4-Cl	CO_2Et	Trans	B	79	148–150 (3.0)	$C_{12}H_{13}ClO_2$
2,4,5-(OMe)$_3$	CO_2Et	Trans	B	71	170–171 (0.8)[b]	$C_{15}H_{20}O_5$
2,5-(OMe)$_2$-4-Me	CO_2Et	Trans	B	65	149–152 (0.7)	$C_{15}H_{20}O_4$
4-Br	$CONHNH_2$	Cis	A	26	122–123	$C_{10}H_{11}BrN_2O$
4-Br	$CONHNH_2$	Trans	B	51	176–177	$C_{10}H_{11}BrN_2O$
4-Cl	$CONHNH_2$	Cis	A	24	110	$C_{10}H_{11}ClN_2O$
4-Cl	$CONHNH_2$	Trans	B	54	164–165[c]	$C_{10}H_{11}ClN_2O$
2,4,5-(OMe)$_3$	$CONHNH_2$	Trans	B	73	125–127	$C_{13}H_{18}N_2O_4$
2,5-(OMe)$_2$-4-Me	$CONHNH_2$	Trans	B	77	142	$C_{13}H_{18}N_2O_3$
4-Br	NH_2	Cis		55	189	$C_9H_{10}BrN \cdot HCl$
4-Br	NH_2	Trans		62	209–210	$C_9H_{10}BrN \cdot HCl$
4-Cl	NH_2	Cis		60	185–187	$C_9H_{10}ClN \cdot HCl$
4-Cl	NH_2	Trans		65	196–198[d]	$C_9H_{10}ClN \cdot HCl$
2,4,5-(OMe)$_3$	NH_2	Trans		46	224–225	$C_{12}H_{17}NO_3 \cdot HCl$
2,5-(OMe)$_2$-4-Me	NH_2	Trans		52	211–213	$C_{12}H_{17}NO_2 \cdot HCl$

[a]All compounds were analyzed either for C, H or C, H, and N. [b]Mp (petroleum ether) 67–68°. [c]Lit.[9] mp 162–163.5°. [d]Lit.[9] mp 195–198°.

yield of **3-(2,5-dimethoxy-4-methylphenyl)butan-2-one**, bp 118–120° (0.8 mm). *Anal.* C, H. Further alkylation gave 84% of **3-(2,5-dimethoxy-4-methylphenyl)-3-methylbutan-2-one**, bp 102–105° (0.05 mm). *Anal.* C, H.

Oximes of the above ketones were obtained by refluxing them for 2 hr with a threefold excess of $NH_2OH \cdot HCl$ with K_2CO_3 in MeOH.

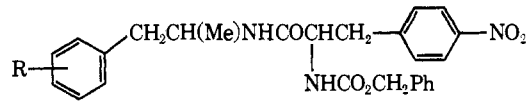
3-(2,5-Dimethoxy-4-methylphenyl)-2-hydroxyiminobutane, obtained in 90% yield, had mp 116–117° (MeOH). *Anal.* C, H, N. **3-(2,5-Dimethoxy-4-methylphenyl)-3-methyl-2-hydroxyiminobutane** had mp 135–136° (MeOH), yield 82%. *Anal.* C, H, N.

Reduction of these oximes with $LiAlH_4$ in THF gave respectively **2-amino-3-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride** (35) [mp 218–219° (*i*-PrOH), yield 76%. *Anal.* C, H, N] and **3-amino-2-(2,5-dimethoxy-4-methylphenyl)-2-methylbutane hydrochloride** [mp 195–196°, yield 64%. *Anal.* C, H, N]. The imine corresponding to the latter compound was also isolated as its hydrochloride during the reduction: mp 158–160° (*i*-PrOH–Et_2O). *Anal.* C, H, N.

(F) Enantiomeric Phenylisopropylamines. The phenylisopropylamine (1 equiv) and *N*-benzyloxycarbonyl-L-phenylalanine *p*-nitrophenyl ester (1 equiv) were heated under reflux for 30 min in the minimum volume of dry EtOAc. The solid which separated was collected, washed with cold EtOAc, and recrystallized from EtOH until there was no change in optical rotation and the nmr signal due to the α-methyl group appeared as a doublet only. This was the pure (−) diastereoisomeric amide (Table IX). The mother liquors were concentrated to dryness *in vacuo*, and the resulting solid, dissolved in $CHCl_3$, was washed with 2 *N* aqueous NaOH until the aqueous layer was colorless and finally washed with H_2O. The $CHCl_3$ solution was dried ($MgSO_4$) and the residue after removal of solvent was recrystallized from EtOH to give the pure (+) diastereoisomeric amide (Table IX). The (+)-amides derived from 2,5-dimethoxy-, 3,4,5-trimethoxy-, and 2,5-dimethoxy-4-methylamphetamine were obtained by conversion of the mother liquors to the parent amphetamine, this partially resolved material then being again reacted with the D isomer of *N*-benzyloxycarboxylphenylalanine *p*-nitrophenyl ester.

The diastereoisomeric amides, suspended in EtOH, were reduced at room temperature and atmospheric pressure over 10% Pd/C catalyst. The mixture was filtered when H_2 uptake was complete, dissolved in dry C_6H_6, and warmed to 40° for 1 hr with PhNCS (1 equiv); the reaction was monitored using silica gel tlc with C_6H_6–Et_2O–MeOH (2:7:1) as solvent. When reaction was

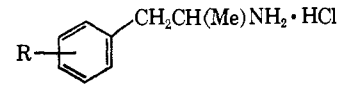
Table IX



R	% yield	No. of times recrystd from EtOH	Mp, °C	$[\alpha]^{25}D$[a]	τ for Me doublet[b]	Formula[c]
3,4-$(OMe)_2$	78	2	187	−5*	9.09, 9.16	$C_{28}H_{32}N_2O_5$
3,4-$(OMe)_2$	73	3	150	+10*	8.99, 9.06	$C_{28}H_{32}N_2O_5$
2,5-$(OMe)_2$	68	3	166	−11*	9.02, 9.08	$C_{28}H_{32}N_2O_5$
2,5-$(OMe)_2$	59	2	168	+11.9*	8.96, 9.00	$C_{28}H_{32}N_2O_5$
3,4,5-$(OMe)_3$	63	2	198	−6	9.08, 9.15	$C_{29}H_{34}N_2O_6$
3,4,5-$(OMe)_3$	63	3	195	+10*	8.96, 9.03	$C_{29}H_{34}N_2O_6$
2,4,5-$(OMe)_3$	67	2	187	−4.5	8.98, 9.05	$C_{29}H_{34}N_2O_6$
2,4,5-$(OMe)_3$	34	3	168–170	+13.5*	8.90, 8.97	$C_{29}H_{34}N_2O_6$
2,5-$(OMe)_2$-4-Me	54	3	196–197	−6	8.97, 9.04	$C_{29}H_{34}N_2O_5$
2,5-$(OMe)_2$-4-Me	50	2	193	+10	8.88, 8.95	$C_{29}H_{34}N_2O_5$

[a]All at C_2 in $CHCl_3$ except those marked * which are at C_4 in $CHCl_3$ (C_2 = concentration of 2 g/100 ml). [b]Measured at 100 MHz using a Jeol JNM-4-H-100 spectrometer. Solutions were made at 10% in $CDCl_3$ using TMS as internal reference; spectra were run at 50°. [c]All compounds were analyzed for C, H, and N.

Table X



R	Enantiomer	% yield from racemate	Mp, °C	$[\alpha]^{25}D$[a]	Formula[b]
3,4-$(OMe)_2$	−	53	135–136	−24*	$C_{11}H_{17}NO_2 \cdot HCl$
3,4-$(OMe)_2$	+	39	137	+22.7	$C_{11}H_{17}NO_2 \cdot HCl$
2,5-$(OMe)_2$	−	46	144	−17	$C_{11}H_{17}NO_2 \cdot HCl$
2,5-$(OMe)_2$	+	37	144	+19	$C_{11}H_{17}NO_2 \cdot HCl$
3,4,5-$(OMe)_3$	−	42	205–206	−18	$C_{12}H_{19}NO_3 \cdot HCl$
3,4,5-$(OMe)_3$	+	62	200	+17.5	$C_{12}H_{19}NO_3 \cdot HCl$
2,4,5-$(OMe)_3$	−	75	159	−20	$C_{12}H_{19}NO_3 \cdot HCl$
2,4,5-$(OMe)_3$	+	9	163	+18.8	$C_{12}H_{19}NO_3 \cdot HCl$
2,5-$(OMe)_2$-4-Me	−	22	196	−17*	$C_{12}H_{19}NO_2 \cdot HCl$
2,5-$(OMe)_2$-4-Me	+	29	197	+16	$C_{12}H_{19}NO_2 \cdot HCl$
2,5-$(OMe)_2$-4-Br	−		145	−12†	$C_{11}H_{16}BrNO_2 \cdot HBr$
2,5-$(OMe)_2$-4-Br	+		144	+13†	$C_{11}H_{16}BrNO_2 \cdot HBr$
2,5-$(OMe)_2$-4-Cl	−		195	−14	$C_{11}H_{16}ClNO_2 \cdot HCl$
2,5-$(OMe)_2$-4-Cl	+		198	+16	$C_{11}H_{16}ClNO_2 \cdot HCl$

[a]All at C_4 in H_2O except those marked * which are at C_5 in H_2O, or † which are at C_2 in H_2O (C_4 = concentration of 4 g/100 ml). [b]All compounds were analyzed for C, H, and N.

complete, C_6H_6 was removed *in vacuo* and the residual gum was dissolved in CF_3CO_2H and kept in a stoppered flask at room temperature for 2 hr. CF_3CO_2H was removed *in vacuo*; the residue was dissolved in 2 *N* HCl and extracted several times with ether. Basification of the aqueous layer (1 *N* NaOH) gave an oil which was extracted into $CHCl_3$, dried ($MgSO_4$), and distilled. The residue, dissolved in EtOH, was acidified by dropwise addition of concentrated HCl, the whole mixture evaporated to dryness *in vacuo*, and the residue recrystallized from EtOH-Me_2CO to give the enantiomeric phenylisopropylamine hydrochlorides (Table X).

The enantiomers of 4-bromo-2,5-dimethoxy- and 4-chloro-2,5-dimethoxyphenylisopropylamine were prepared by bromination and chlorination, respectively, of the enantiomers of 2,5-dimethoxyphenylisopropylamine, using the procedures outlined in section A.

Pharmacology. (A) Rabbit Rectal Temperature. The method is similar to that described by Brimblecombe.[25] Rectal temperature was measured in Old English rabbits (1.9–2.4 kg), restrained in wooden containers, using copper-constantan thermocouples inserted about 4 cm into the rectum. The temperature was recorded continuously over a period of 5 hr with a Honeywell Brown 12-channel recorder. Reference thermocouples were maintained at 37° and the ambient temperature was kept as constant as possible at 20°. Prior to injection the rabbits were placed in the restraining cages and left until their temperature was steady, groups of four to six animals being used for each dose level. Drugs were administered as solution in sterile physiological saline by injection into a marginal ear vein, using a volume of 0.5 ml/kg.

The potencies of drugs in elevating rectal temperature were expressed relative to DOM using a 5–6 point assay procedure by one of two procedures. Method A employed the maximum temperature reached at a particular dose level as the basis for comparison. Method B measured the integrated area under the time-temperature curve. This was achieved by plotting increases in temperature at 20-min intervals over a period of 240 min and joining the points by a straight line (Figure 1).

Dose-response curves were plotted for DOM (Figure 2) and the dose required to elevate the temperature by 1° was obtained by extrapolation. The doses of other drugs required to elevate temperature by 1° were calculated from their potency relative to DOM as determined by method A.

(B) Cat EEG. Stainless steel screw electrodes were aseptically implanted in cats over the lateral and suprasylvian gyri of the cerebral cortex, as described by Bradley and Elkes.[35] After the operation the animals were allowed to recover for 2 weeks before use. For recording purposes the cats were placed in a sound-attenuated chamber and observed by closed circuit television. After a period of acclimatization of 1 hr, the drug, dissolved in sterile physiological saline, was administered intramuscularly; doses of drugs were given incrementally to the same animal at 30-min intervals using a common dose ratio of 2. When the drugs produced

hypersynchronous 4-6-Hz large-amplitude activity in the EEG, an auditory stimulus of 1000-Hz 80 dB intensity was presented through a loud speaker mounted in the cavity of the chamber. This stimulus elicited a standard behavioral response in which the cat opened its eyes wide and raised or turned its head toward the source of the sound. Some cats tended to become habituated rather readily to the stimulus, and to overcome this it was necessary to change the frequency of the stimulus at intervals. This standard behavioral response was invariably accompanied by full desynchronization (low amplitude, high frequency activity) in the EEG, but at certain dose levels the 4-6-Hz activity reappeared immediately after the stimulus was switched off ("phasic" EEG response) (see Figure 3). In order to quantify the EEG response produced by the drugs, the dose required to elicit the "phasic" EEG response between the bursts of hypersynchronous 4-6-Hz activity was determined.

(C) **Open-Field Test.** The procedure adopted was essentially that of Brimblecombe,[25] using an open-field apparatus of the design described by Broadhurst.[36] The arena was circular with a diameter of 82 cm; it was illuminated by four 150-W lamps and had a background white noise level of 88 dB. With the exception of LSD, which was injected 15 min before testing, the drugs were administered subcutaneously to groups of eight rats 1.5-3 hr before the animals were placed in the open field for a 3-min test period. Control animals received an equivalent volume of physiological saline. During the test period the rats were scored according to the number of times they reared, preened, and defaecated, the number of faecal boluses passed, the number of floor squares traversed at the periphery, and, separately, the number of squares traversed in the central part of the field. The significance of the mean occurrence of these various activities, compared to the control group, was assessed using Student's t test. Doses quoted in Table II are the lowest at which significant effects were detected.

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