Silicon-Containing Phenethylamines

MAX FRANKEL,[1] MORDECHAI BROZE, DAVID GERTNER, AVNER ROTMAN, AVINOAM SHENHAR, AND ALBERT ZILKHA

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

Received January 31, 1968

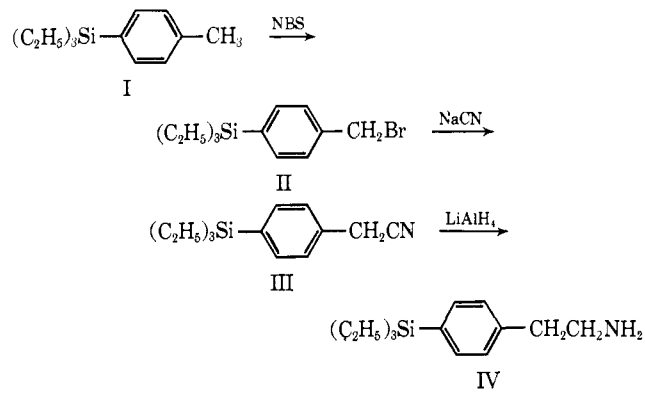
p-Trimethylsilyl- and *p*-trimethylsilylmethylphenethylamine were obtained by $LiAlH_4$ reduction of the nitriles, prepared from the respective benzyl halides and NaCN. DL-1-*p*-Trimethylsilylmethylphenyl-2-aminopropane, a silicon analog of amphetamine, was also prepared. Preliminary pharmacological evaluation of ten such phenethylamines containing silyl groups at various positions in the aromatic nucleus showed that the *p*-silyl-substituted phenethylamines, contrary to the *ortho* and *meta* isomers, had a blood pressure lowering activity, the extent of which depended on the type of substituents attached to the silicon. *p*-Trimethylsilyl- and *p*-trimethylsilylmethylphenethylamine were found to have also a wide spectrum of antibacterial activity as compared to phenethylamine.

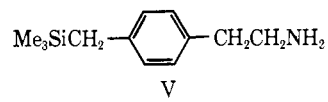
We wish to report on experiments undertaken to study the effect of the introduction of trisubstituted-silyl groups at various positions on the ring of phenethylamines. On the one hand, the silyl groups are bulky, and as mentioned, may produce a depressor effect. On the other hand, these groups have an electron-withdrawing effect which can affect the resistance of the phenethylamine toward biological oxidation. The introduction of a methylene group between the trimethylsilyl group and the nucleus stabilizes the compound to electrophilic attack.[2] The phenethylamines containing trisubstituted-silyl groups can be expected to have physical properties, *e.g.*, solubility, partition coefficient, and permeability to physiological membranes, different from the analogous compounds not containing silicon. This may have a bearing on the biological effects of these compounds.

We have previously reported the synthesis of a number of phenethylamines having a trimethylsilyl group at various positions of the aromatic nucleus.[3] Preliminary biological evaluation of the compounds showed interesting depressor activity especially for the *para*-substituted derivatives. These findings prompted us to synthesize other phenethylamines containing still bulkier trisubstituted silyl groups such as dimethyl-*p*-tolylsilylphenethylamine,[4] dimethylbis(*p*-β-aminoethylphenyl)silane,[4] *p*-triethylsilylphenethylamine, *p*-trimethylsilylmethylphenethylamine, and DL-1-*p*-trimethylsilylmethylphenyl-2-aminopropane. The synthesis of the last three is reported here.

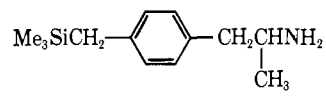
Triethyl-*p*-tolylsilane (I)[5] was converted to *p*-triethylsilylbenzyl bromide (II) by reaction with N-bromosuccinimide. The bromide (II) was converted to the cyanide (III) by reaction with sodium cyanide and reduced with $LiAlH_4$ to *p*-triethylsilylphenethylamine (IV).

p-Trimethylsilylmethylbenzyl chloride[6] was converted to the respective nitrile by heating with NaCN in DMSO, which in turn was reduced to *p*-trimethylsilylmethylphenethylamine (V). Hydrolysis of the nitriles gave the respective phenylacetic acids.





DL-1-*p*-Trimethylsilylmethylphenyl-2-aminopropane (DL-*p*-trimethylsilylamphetamine, VI) was obtained by the reaction of *p*-trimethylsilylmethylbenzylmagnesium chloride with acetonitrile and reduction of the intermediate imine with $LiAlH_4$.[7]



Preliminary Biological Evaluation.—The following silicon-containing phenethylamines were tested on cats or guinea pigs for blood pressure effects; hydrochlorides were used in their aqueous solutions. *p*-Trimethylsilylphenethylamine hydrochloride (**1**), *o*-trimethylsilylphenethylamine hydrochloride (**2**), *m*-trimethylsilylphenethylamine hydrochloride (**3**), *p*-triethylsilylphenethylamine hydrochloride (**4**), *p*-(dimethyl-*p*-tolylsilyl)-phenethylamine (**5**), dimethylbis(*p*-β-aminoethylphenyl)silane (**6**), N,N-dimethyl-*p*-trimethylsilylphenethylamine hydrochloride (**7**), β-(*p*-trimethylsilylphenyl)-*n*-propylamine hydrochloride (**8**), DL-(*p*-trimethylsilyl)-amphetamine hydrochloride (**9**), and *p*-trimethylsilylmethylphenethylamine hydrochloride (**10**).

The preliminary pharmacological results (Table I) show that the compounds having a trisubstituted-silyl

(1) Dedicated to Professor Th. Reichstein in sincere appreciation on the occasion of his seventieth birthday.

(2) C. Eaborn, "Organosilicon Compounds," Butterworth and Co. Ltd., London, 1960, p 145.

(3) M. Frankel, M. Broze, D. Gertner, and A. Zilkha, *J. Chem. Soc., C*, 379 (1966).

(4) A. Rotman, D. Gertner, and A. Zilkha, *Can. J. Chem.*, **45**, 1957 (1967).

(5) R. A. Benkesser and H. Landesman, *J. Am. Chem. Soc.*, **76**, 904 (1954).

(6) N. S. Nametkin, A. V. Topchiev, and N. A. Pritula, *Issled. v Obl. Kremniiorgan. Soedin., Sintez i Fiz.-Khim. Svoistva, Akad. Nauk SSSR, Inst. Neftekhim. Sinteza, Sb. Statei*, 156 (1962); *Chem. Abstr.*, **59**, 3943 (1963).

(7) A. Rohland and H. R. Sullivan, *J. Am. Chem. Soc.*, **75**, 5898 (1953).

TABLE I
EFFECTS ON BLOOD PRESSURE AND RESPIRATION RATE IN CATS AND GUINEA PIGS[a,b]

Compd	Animal	Dose, mg/kg	Changes in blood pressure, mm	Duration, min	Change of resp rate, %
Phenethylamine HCl	Cat	0.5	+50	5	+5
		1	+60	5	+5
		2	+75	6	+10
1	Guinea pig	0.1	−10	15	+130
		0.5	−15	15	+300
		1	−25	15	+300
		2	−35	15	+330
	Cat	0.5	−30	1	+40
		1	−50	3	+150
		2	−60	7	+220
		5	−100	8	
2	Cat	0.5	+40	4	
		1	+80	5	−10
		2	+80	10	−15
3	Cat	0.5	+20	10	−30
		1[c]	+30	12	−40
		2[c]	+50	15	−60
4	Cat	5	−130[d]	150	Not tested
5[e]	Cat	0.5	−50	1	+33
		1	−65	3	+22
		2	−120	3.5	+600
6[e]	Cat	1	...	...	+9
		3	−5	1	+42
		7	−20	4	+175
7	Cat	1	−10	1	...
		2	−50	1.5	+5
8	Guinea pig	1	...	...	...
		5	−20	20	+350
	Cat	0.5	−15	1	...
		1	−30	1.5	+130
		2	−50	1	+140
		3	−80	7	+250
		5	−100	5	
		10	−130	*f*	
9	Cat	0.5	−10	1	+15
		1	−40	1	+40
		2	−70	30	+250
10	Cat	0.5	−30	3	+300[g]
		1	−40	3	+300[g]
		2	−60	5	+250[g]

[a] Tests were performed on anesthetized (pentobarbital 30 mg/kg iv) cats and anesthetized (urethan 1.3 g/kg ip) guinea pigs. Three animals were tested for each dose level. The starting blood pressure was between 120 and 130 mm. [b] No significant changes were observed on heart rate. [c] Apparently toxic dose, because after administration there was dyspnea, followed by prolonged upnea, and cardiac irregularities, and after an initial rise a precipitous fall in blood pressure resulted in death. [d] Also found ECG bradycardia, T inversion, and extrasystole, dyspnea, and increased mucus secretion from lungs. [e] Compound was administered in propylene glycol solution. [f] Animals succumbed following the injection. [g] After bilateral vagotomy only a slight increase was observed.

TABLE II
DOSE RANGE FINDING EXPERIMENTS AND GROSS BEHAVIORAL CHANGES (MICE)[a]

Compd	Dose, mg/kg	General changes
2	5	No obvious changes.
	15	Hyperactivity lasting about 1 hr.
	25	Hyperactivity lasting 2 hr.
	50	Hyperactivity changing into sudden extreme outbursts; constant gnawing. At times circling movements; symptoms lasting 4 hr.
	100	Same as above, but symptoms more intensified.
	200	Animals died within 5 min of injection.
3	5	No obvious changes.
	15	Hyperactivity.
	25	Hyperactivity; slight tremors.
	50	Strong hyperactivity, strong tremors. Piloerection; effects lasting 2 hr.
	100	Animals died within 10 min of injection.
7	15	No obvious changes.
	25	Hyperactivity.
	50	Strong hyperactivity lasting about 1 hr.
	100	Strong hyperactivity, slight tremors. Piloerection lasting about 1 hr.
	200	Animals died within 5 min of injection.
10	15	No obvious changes.
	25	Slight sedation lasting 45 min.
	50	Slight sedation lasting 1.5 hr.
	100	Animals died within 45 min of injection.

[a] The tests were conducted on male Albino mice. The substances were administered intraperitoneally using five animals for each dose level and any gross behavioral changes were noted.

group in the *para* position have a blood pressure lowering activity, whereas the *ortho* and the *meta* derivatives exhibited a hyperpressor activity similar to phenethylamine. It seems that the pressor activity of the *ortho*-substituted phenethylamine (**2**) is greater than that of the *meta* (**3**). Heart rate was not affected by injection of these compounds. Respiration rate increased on injection of the *para*-substituted compounds, while the *meta* and the *ortho* compounds lowered the respiration rate (Table I).

Among the compounds which were depressors, *p*-triethylsilylphenethylamine (**4**) had the strongest effect, both on lowering the blood pressure and on the duration of activity. Another interesting feature is that introduction of a methyl group on the α-carbon atom of the aliphatic side chain did not influence the blood pressure activity. On the other hand, (DL-*p*-trimethylsilyl)amphetamine (**9**) which has a methyl group in the β position showed more extended action as compared with *p*-trimethylsilylphenethylamine. The introduction of a methylene group between the trimethylsilyl group and the benzene ring did not change significantly the blood pressure lowering activity (compare **1** and **10**, Table I).

Antagonistic effects on hypertension caused by epinephrine were tested on **7** and **10**. It was found that they did not affect the pressor effect of epinephrine.

Gross behavioral changes for **2**, **3**, **7**, and **10** were conducted on mice (Table II). The phenethylamines **1**, **8**, and **9** had a weak psychotropic effect (Table III). These three compounds also did not reverse the reserpine motor activity depression in contrast to amphetamine which caused complete reserpine reversal.

The antibacterial activity of **1** and **10** was evaluated on some types of bacteria and fungi. Compound **1** inhibited growth of bacteria at concentrations of 500 μg/ml and **10** at 100 μg/ml, whereas phenethylamine hydrochloride did not cause inhibition at the same conditions even at concentrations of 1000 μg/ml. In the presence of 50% blood in the growth media, the antibacterial activity of **10** was reduced considerably.

TABLE III
PSYCHOTROPIC TESTS

Compd	Dose, mg/kg	Rotating rod,[a] % redn in performance after[b] 15 min	30 min	Activity cage,[c] % redn[d]	Meriones digging —test[e] results after[f]— 30 min	60 min	Conditioned avoidance response,[g] % redn ip	sc
1	5						3	
	10			0	1/4	0/4	11	
	20	0	0	24	4/4	3/4	30	0
	40	40[h]	0	29			75	2
8	5						3	
	10			25	2/4	0/4	35	
	20	0	0	27	3/4	4/4	61	
	40	0	0	37[i]			74	0
9	20	0	0[h]					

[a] Carried out on six mice per group, intraperitoneal injection (N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc.*, **46**, 208 (1957). [b] No reduction in performance was observed after 60 or 90 min. [c] Ten mice were used for each dose level; 30 min following intraperitoneal injection of the examined compounds, the mice were tested individually for 10 min in a photoelectric circular activity cage. Controls were injected with saline. [d] Average per cent reduction of activity 30 min after injection. [e] Carried out on 4 meriones per dose level, intraperitoneal injection [*Triangle. Sandoz J. Med. Sci.*, **4**, 244 (1960)]. [f] Numerator indicates number of animals which did not dig. Denominator indicates number of animals injected. [g] Three rats per dose level were tested. Average per cent reduction 1 hr after injection [D. Bovet, L. Gatti, and M. Frank, *Sci. Rept. Ist. Super. Sanita*, **1**, 127 (1961)]. [h] Slight piloerection was observed. [i] Under identical conditions, amphetamine (10 mg/kg ip) increased motor activity by 70%.

Experimental Section[8]

Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

***p*-Triethylsilylbenzyl Bromide.**—N-Bromosuccinimide (69.5 g, 0.39 mole) was added to a stirred solution of *p*-triethylsilyltoluene (85 g, 0.41 mole) in dry CCl_4 (350 ml), followed by dibenzoyl peroxide (1 g), and heated to reflux to start the bromination. The reaction mixture was heated for 2 hr and cooled in ice and the succinimide which formed was filtered off. The filtrate was washed thoroughly (4% NaOH, H_2O), dried ($CaCl_2$), and distilled. The product (81 g, 70%) distilled at 145° (3 mm). *Anal.* ($C_{13}H_{21}BrSi$) C, H, Br, Si.

***p*-Triethylsilylbenzyl Cyanide.**—To a stirred solution of NaCN (13 g, 0.26 mole) in H_2O (15 ml), *p*-triethylsilylbenzyl bromide (34 g, 0.12 mole) in EtOH (30 ml) was added and the mixture was stirred and heated under reflux for 6 hr. EtOH was removed *in vacuo*, and the salts were filtered off and washed with Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and fractionally distilled. The cyanide (19.5 g, 71%) distilled at 149° (1.5 mm), 130° (0.5 mm). *Anal.* ($C_{14}H_{21}NSi$) C, H, N, Si.

***p*-Triethylsilylphenethylamine.**—A solution of *p*-triethylsilylbenzyl cyanide (7 g, 0.03 mole) in dry Et_2O (80 ml) was dropped with stirring under argon into a suspension of $LiAlH_4$ (1.7 g, 0.045 mole) in dry Et_2O (120 ml) and heated under reflux for 3 hr. The reaction mixture was cooled to −15°, and cold H_2O (3.3 ml, 0.18 mole) was dropped in cautiously to destroy excess reagent, stirred for 30 min, and filtered. The precipitate was extracted thoroughly with CH_2Cl_2. The organic layer and extracts were combined, dried (Na_2SO_4), and distilled *in vacuo*. The amine (4.2 g, 59%) distilled at 122° (0.5 mm), 128° (1 mm). *Anal.* ($C_{14}H_{25}NSi$) C, H, N, Si.

Dry HCl was passed through a solution of *p*-triethylsilylphenethylamine (1 g) in dry Et_2O for 3 min. The hydrochloride precipitated out in quantitative yield, was collected, and washed with dry Et_2O; mp 130°. *Anal.* ($C_{14}H_{26}ClNSi$) C, H, N, Cl.

***p*-Triethylsilylphenylacetic Acid.**—A solution of KOH (2.5 g, 0.044 mole) in H_2O (4 ml) was added to *p*-triethylsilylbenzyl cyanide (3 g, 0.013 mole) in diethylene glycol (24 ml), and the mixture was heated under reflux for 10 hr. The solution was cooled, acidified with 5% HCl to pH 1, and extracted with Et_2O, and the extract was washed with H_2O to remove diethylene glycol. The organic acid was taken up in 4% NaOH solution, precipitated with cold 5% HCl, extracted with Et_2O, dried (Na_2SO_4), and distilled *in vacuo*; bp 170° (1.5 mm), mp 24°, yield 2.4 g (74%). *Anal.* ($C_{14}H_{22}O_2Si$) C, H, Si.

***p*-Trimethylsilylmethylbenzyl Cyanide.**—*p*-Trimethylsilylmethylbenzyl chloride[6] (42.5 g, 0.2 mole) was dropped during 10–15 min into a stirred solution of NaCN (10.6 g, 0.216 mole) in DMSO (50 ml) at 40–50°. The reaction mixture was stirred at 40–50° for 3 hr, cooled, diluted with H_2O (150 ml), and extracted thoroughly with Et_2O (six 50-ml portions). The combined ethereal extracts were washed with 6 *N* HCl, H_2O, and dried ($MgSO_4$). The Et_2O was removed *in vacuo* and the product (39 g, 97%) was distilled at 134–136° (5 mm). *Anal.* ($C_{12}H_{17}NSi$) C, H, N. When the reaction was carried out in H_2O–EtOH, lower yields of the nitrile were obtained.

***p*-Trimethylsilylmethylphenethylamine.**—*p*-Trimethylsilylmethylbenzyl cyanide (20.3 g, 0.1 mole) in dry Et_2O (170 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (5.1 g, 0.134 mole) in dry Et_2O and heated under reflux for 22 hr. Excess reactant was destroyed with a 20% solution of sodium tartrate. The ethereal layer was separated and washed with tartrate solution, dried ($MgSO_4$), and distilled. The amine (15 g, 73%) was collected at 109° (3 mm). *Anal.* ($C_{21}H_{21}NSi$) C, H, N.

The amine hydrochloride, mp 169°, was obtained as before. *Anal.* ($C_{12}H_{22}ClNSi$) C, H, N, Cl, Si.

***p*-Trimethylsilylmethylphenylacetic Acid.**—*p*-Trimethylsilylmethylbenzyl cyanide (1 g) in AcOH (1 ml) and 1:1 H_2SO_4 (2 ml) was heated under reflux for 3 hr. H_2O (12 ml) was added, the aqueous layer was decanted off, and the crude phenylacetic acid crystallized out. It was purified by dissolving in dilute Na_2CO_3 and precipitating with acid, yield 0.71 g (65%), mp 72° after recrystallization from petroleum ether (bp 40–60°). *Anal.* ($C_{12}H_{18}O_2Si$) C, H, Si.

DL-1-*p*-Trimethylsilylmethylphenyl-2-aminopropane (**DL-*p*-Trimethylsilylmethylamphetamine**).—A solution of *p*-trimethylsilylmethylbenzyl chloride (15.9 g, 0.0745 mole) in dry Et_2O (45 ml) was dropped in with stirring to Mg turnings (1.83 g, 0.075 g-atom) in dry Et_2O (8 ml) and heated under reflux for 2 hr. MeCN (2.67 g, 0.06 mole) in dry Et_2O (6 ml) was added, and the reaction mixture was heated under reflux for 4 hr. A slurry of $LiAlH_4$ (2.82 g, 0.074 mole) in dry THF (28 ml) was added slowly and the mixture was boiled under reflux for 8 hr. The solvents were removed *in vacuo*, and dry Et_2O was added to the residue followed by a solution of sodium potassium tartrate until two phases were formed. The Et_2O solution was separated, washed with tartrate solution, dried ($MgSO_4$), and distilled. The product (4.2 g, 31%) was collected at 125 (5 mm). *Anal.* ($C_{13}H_{23}NSi$) C, H, N.

Pharmacological Evaluation.—Experiments on the effects on blood pressure, heart rate, and respiration rate, due to the silicon-containing compounds, were carried out on cats or guinea pigs as described previously.[9] The compounds were injected into the left femoral vein. Blood pressure was measured from a carotid artery and recorded on a kymograph. The electrocardiogram was recorded using needle electrodes secured under the skin. Respiration was recorded by means of a thermocouple inserted into a tracheal cannula and connected to a polygraph.

(8) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(9) I. Belsky, D. Gertner, and A. Zilkha, *J. Med. Chem.*, **11**, 451 (1968).

Reversal of reserpine effects of compounds **1**, **8**, and **9** were tested. Reserpine (25 mg/kg) was injected subcutaneously to groups of mice (five per group); 3 hr later the compounds were injected intraperitoneally in doses of 10, 20, and 30 mg/kg. Controls were injected with DL-amphetamine (20 mg/kg ip) which caused complete reserpine reversal, *i.e.*, arousal from sedated state and cessation of ptosis. This reversal lasted for at least 3 hr and after that period the animals again returned to the sedated state. Compound **9** (20 mg/kg) showed a very slight, delayed, and short-lasting reserpine reversal.

Antagonistic action to pressor activity of epinephrine was tested as follows. Epinephrine (1–2 μg/kg) was administered to cats (2.5–3.5 kg) and when the blood pressure returned to control level the test substance was administered. Five minutes later epinephrine was injected and the effects were compared.

Gross behavioral changes were conducted on mice. Substances were administered intraperitoneally into groups of five animals for each dose level and changes were noted. Observations were made for not more than 24 hr after injection.

Antibacterial Tests.—Compound **1** was tested for antibacterial activity on the following bacteria and fungi: *Staphylococcus aureus* 209P (Oxford), *S. aureus* 183, *Bacillus cereus*, *B. cereus I*, *Escherichia coli* W, *E. coli* WI, *E.* $O_{111}B_4H_{12}$, *E. coli* $O_{119}B_2H_6$, *Salmonella typhimurium*, *Shigella flexneri* 4b 5412, *Candida albicans*, and *Cryptococcus neoformans* A. The bacteria and the fungi (1×10^4 and 1×10^6) were added in drops (0.02 ml) to Petri dishes containing the growth media, composed of Agar 3 (containing peptone, yeast extract, beef extract, dextrose, and buffer pH 7) or Saboraud agar and 0.4% yeast extract. Control experiments were carried out wherein the bacteria or the fungi were grown in the absence of the compound investigated. Phenethylamine hydrochloride did not inhibit growth at concentrations of 1000 μg/ml, while **1** inhibited growth of the above bacteria at 500 μg/ml, of *C. neoformans* A at 1000 μg/ml, and of *C. albicans* at 500 μg/ml (10^4) and 1000 μg/ml (10^6).

Compound **10** was tested for antibacterial activity in the above growth media and on addition of 50% human or sheep blood to the growth media. The results are summarized in Table IV. It is seen that **10** inhibited most of the bacteria tested at a concentration of 100 μg/ml, but in the presence of blood the activity was lower. Compound **10** did not inhibit the growth of *C. albicans* and *C. neoformans* A at concentrations of 100 or 200 μg/ml.

TABLE IV
ANTIBACTERIAL ACTIVITY[a] OF *p*-TRIMETHYLSILYLMETHYLPHENETHYLAMINE HYDROCHLORIDE (**10**)

Type of bacteria or fungi	Concn of compd,[b] μg/ml	Inhib of growth Concn of bacteria 10^4	Inhib of growth Concn of bacteria 10^6	Inhib in presence of 50% human blood[c] Concn of bacteria 10^4	Inhib in presence of 50% human blood[c] Concn of bacteria 10^6
S. aureus 209P (Oxford)	100	+ −	+ +	+ +	−
	200	+ −	+ +	+ +	+ +
S. aureus 183	100	−	−	−	−
	200	+ +	+ +	+ +	+
B. cereus	100	+ +	+ +	−	−
	200	+ +	+ +	+	−
B. cereus (streptomycin resistant)	100	−	−		−
	200		+ +		−
E. coli $O_{111}B_4H_{12}$	100	+ +	+ +	−	−
	200	+ +	+ +	+ +	+ +
E. coli $O_{119}B_4H_{12}$	100	+ +	+ +	−	−
	200	+ +	+ +	+ +	+ +
S. typhimurium	100	− +	+ −	−	−
	200	− +	+ +	−	−
Shigella flexneri 4b 5412	100	+ +	+ +	−	−
	200	+ +	+ +	+ +	+ +
Candida albicans	100	−	−	−	−
	200	+	−	−	−
Cr. neoformans "A"	1000	−	−	−	−
	200	−	−	+	−

[a] ++, complete inhibition; +, partial inhibition; −, no inhibition. [b] No inhibition was observed at a concentration of 50 μg/ml. [c] With *C. albicans* and *Cr. neoformans* "A" 50% sheep blood was used.

Acknowledgment.—We wish to thank Dr. H. Edery and Dr. Y. Grunfeld of the Israel Institute for Biological Research, Ness-Ziona, and the Pharmacological Institute of the National Council for Research and Development for carrying out the pharmacological tests. Likewise, our thanks are due to Dr. M. Aharonson and his staff at the Israel Institute for Biological Research, Ness-Ziona, for carrying out the bacteriological tests. This research was partly supported by "Yissum" Research Development Co.

A Conformational Study of β-Phenethanolamine Receptor Sites. I. The Syntheses of the 3-Amino-2-phenyl-*trans*-2-decalols[1]

EDWARD E. SMISSMAN AND WILLIAM H. GASTROCK[2]

School of Pharmacy, University of Kansas, Lawrence, Kansas 66045

Received October 26, 1967
Revised Manuscript Received February 10, 1968

The synthesis of the four possible 3-amino-2-phenyl-*trans*-2-decalols (**1**–**4**) is described. The results of adrenergic α-receptor site stimulation are recorded.

In any biologically active agent which possesses more than one type of action or which is metabolized by more than one pathway, the possibility exists that the approach and binding to a receptor site will require or favor a specific conformation for each effector site, metabolic site, transport, etc. The first attempt to illustrate this postulate involved the use of analogs of acetylcholine in the decalin system and was successful.[3] The application of a similar system to the β-phenethanolamines involves somewhat more complex chemistry but a similar approach.

LaPidus and coworkers[4] have demonstrated that a steric relationship exists among the enantiomorphs of ephedrine and ψ-ephedrine with regard to agonist and

(1) Presented before the 2nd Annual Midwest Regional American Chemical Society Meeting, Lawrence, Kansas, Oct 27–28, 1966.

(2) Taken in part from the dissertation presented by W. H. Gastrock, Feb 1967, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(3) E. E. Smissman, W. L. Nelson, J. B. LaPidus, and J. L. Day, *J. Med. Chem.*, **9**, 458 (1966).

(4) J. B. LaPidus, A. Tye, P. Pait, and B. A. Modi, *ibid.*, **6**, 76 (1963).