Table II. Analgetic Activity of Carbinols of Structure III (R^1, R^2 = Me)

	Analgetic activity, rat tail pressure, ED_{50}, mg/kg sc				
R^3	R^4 = H	R^4 = Me	R^4 = Et	R^4 = *n*-Pr	R^4 = *n*-Bu
Me	0.45	16	>100[a]		>100
Et	0.15	>100[a]	>100		>100[a]
n-Pr	0.034	1.8[a]			
n-Bu	0.036	27	11	20	13
Cyclohexyl	0.056	20	>100[a]	27[a]	>100[a]
CH_2Ph	0.057	7.6	>100[a]	5[a]	13
Morphine ED_{50} 1.7 mg/kg sc, 1.3 mg/kg ip					

[a]Injected intraperitoneally as a suspension of the base in saline.

oripavine series, it has been suggested†,[6] that the receptor surface is even more extensive and that a C-7 substituent binds with a second lipophilic site. If C-15 and C-16 do indeed fit into a "hole" in the receptor, substitution at one of these centers would be expected to hinder the fit of the drug molecule at the receptor with consequent reduction in analgetic potency. All the 16-alkyl-6,14-*endo*-ethenotetrahydrothebaines are, indeed, far less active as analgetics than the unsubstituted compounds. A comparison of analgetic activities of the 16-alkyl and the 16-H compounds in the tetrahydrothebaine series is given in Table II. The introduction of a 16-methyl group resulted in a marked reduction in analgetic effect although, in general, there was still a small residual activity. A group larger than methyl eliminated analgetic activity completely in the carbinols of lower activity (III, R^3 = Me or Et), but weak activity was still observed in some derivatives of the more potent carbinols (III, R^3 = *n*-Bu or CH_2Ph). The results agree with the suggestion that the C-7 substituent plays a part in attaching these drugs to the receptor. A 16-phenyl, benzyl, or phenethyl group eliminated all analgetic activity.

One of the 16-alkyl compounds **48** showed morphine antagonist action, ED_{50} 0.11 (0.05-0.26) mg/kg sc, when tested by the method of Green and Young[7] in rats.

Three members of this series, compounds **17**, **19**, and **47**, possess interesting antitussive activity[8] when assessed orally in guinea pigs by the method of Winter and Flataker.[9]

†K. W. Bentley and J. W. Lewis, reported to the Committee on Problems of Drug Dependence, Feb 1968.

Experimental Section

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, the results obtained for those elements were within ±0.4% of the theoretical values. The structures of all compounds were assigned on the basis of compatible ir and nmr spectra. The iminium perchlorates II were prepared from the 15,16-dide-hydro compounds as previously described.[2] In general, the salts were used without purification or characterization.

General Methods for the Preparation of the 16α-Alkyl Carbinols (III). In method A the iminium perchlorate IIa (0.1 mol) was added portionwise to a stirred solution of RMgX (0.3 mol) in Et_2O (500 ml) and the mixture was stirred and boiled for 18 hr. Saturated aqueous NH_4Cl solution was added and the Et_2O layer was separated and evaporated to give the 16α-alkyl compound. Method B used RLi instead of the Grignard reagent. The carbinol IIIa was also prepared by reaction of MeMgI with the 7α-acetyl compound IIb (method C) or the 7α-carbethoxyl compound IIc (method D).

Demethylation of the 3-methyl ethers III (R^1 = Me) with alkali in diethylene glycol at 210° gave[10] the corresponding tetrahydrooripavines III (R^1 = H) (method E). Reaction of the *N*-methyl carbinols III (R^2 = Me) with CNBr and treatment of the cyanamide with alkaline diethylene glycol at 170° gave[10] the nor bases III (R^2 = H). These were alkylated by standard methods[10] to give N-substituted derivatives (method F).

References

(1) J. W. Lewis and M. J. Readhead, *J. Med. Chem.*, 16, 84 (1973) (paper 29).
(2) D. I. Haddlesey, J. W. Lewis, P. A. Mayor, and G. R. Young, *J. Chem. Soc., Perkin Trans. 1*, 872 (1972).
(3) K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, 89, 3273 (1967).
(4) D. I. Haddlesey, J. W. Lewis, and P. A. Mayor, *J. Chem. Soc., Perkin Trans. 1*, 875 (1972).
(5) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, 6, 986 (1954).
(6) J. W. Lewis, K. W. Bentley, and A. Cowan, *Annu. Rev. Pharmacol.*, 11, 241 (1971).
(7) A. F. Green and P. A. Young, *Brit. J. Pharmacol. Chemother.*, 6, 572 (1951).
(8) A. L. A. Boura, D. I. Haddlesey, E. J. R. Harry, J. W. Lewis, and P. A. Mayor, *J. Pharm. Pharmacol.*, 20, 961 (1968).
(9) C. A. Winter and L. Flataker, *J. Pharmacol. Exp. Ther.*, 112, 99 (1954).
(10) K. W. Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, 89, 3281 (1967).

A Conformational Study of Phenethylamine Receptor Sites. 1. Syntheses of Semirigid Analogs of β-Methylamphetamine

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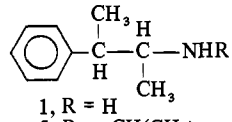
The syntheses of *dl-threo*- and *dl-erythro*-2-amino-3-phenylbutane (**1** and **2**), *threo*- and *erythro*-2-isopropylamino-3-phenylbutane (**5** and **6**), *dl-cis*- and *dl-trans*-2-phenylcyclohexylamine (**3** and **4**), and *dl-cis*- and *dl-trans*-2-phenylcyclohexylisopropylamine (**7** and **8**) are described. The results of the toxicity and behavioral studies are discussed.

In order to investigate the possibility that amphetamine exists in specific conformations at different receptor surfaces as an explanation for the variety of physiological effects observed when this compound is administered, the phenethylamine nucleus has been incorporated into semirigid and rigid systems. The systems utilized in this study are those previously employed in these laboratories in investigating cholinergic and adrenergic receptor sites.[1-8]

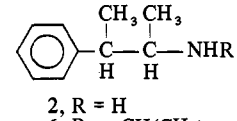
The synthesis and preliminary biological testing of semirigid analogs of β-alkylamphetamines are the subject of this report. The racemic *threo*- and *erythro*-2-amino-3-phenylbutanes (**1** and **2**) and the racemic *cis*- and *trans*-2-phenylcyclohexylamines (**3** and **4**) afford systems which have a certain degree of restriction to rotation about the carbon-carbon single bond to which the phenyl and amino groups are attached. Compounds **1-4** were converted to the

†Taken in part from the dissertation presented by T. L. Pazdernik, Aug 1971, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

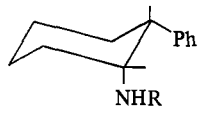
N-isopropyl-β-methylamphetamine analogs **5–8** since the presence of a bulky group on the amino function of amphetamine-like compounds (*e.g.*, furenorex, benzphetamine) decreases the central nervous system stimulation and cardio-



1, R = H
5, R = –CH(CH$_3$)$_2$



2, R = H
6, R = –CH(CH$_3$)$_2$

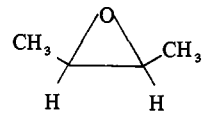


3, R = H
7, R = –CH(CH$_3$)$_2$

4, R = H
8, R = –CH(CH$_3$)$_2$

vascular effects while maintaining the anorexic properties.[9]

The synthesis of the 2,3-disubstituted butane analogs was accomplished *via* epoxidation of *cis*- and *trans*-2-butene to afford *cis*- and *trans*-2-butene oxide (**9** and **10**), respectively, according to the procedure of Pasto and Cumbo.[10]



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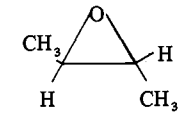

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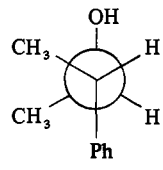

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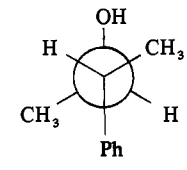

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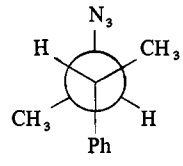

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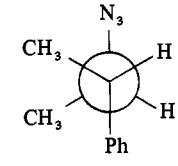

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SN2 opening of the epoxide rings of **9** and **10** with phenyllithium afforded the corresponding *threo*- and *erythro*-3-phenyl-2-butanols (**11** and **12**). The structural assignments were verified by their nmr spectra and by comparing their physical properties with those of *threo*- and *erythro*-3-phenyl-2-butanol (**11** and **12**) prepared by Cram[11] *via* a different synthetic pathway.

The *threo*- and *erythro*-3-phenyl-2-butanols (**11** and **12**) were treated with *p*-toluenesulfonyl chloride in pyridine to afford *threo*- and *erythro*-3-phenyl-2-butyl tosylates which were then converted to the azides **13** and **14**.

The SN2 displacement reaction with sodium azide resulted in 100% inversion of configuration, which is in agreement with the work of Cram, *et al.*,[11-13] in which the ammonlysis of 3-phenyl-2-butyl tosylate occurred with simple inversion (bimolecular reaction involving ammonia and sulfonate ester). Retention of configuration *via* phenyl group participation is only important in solvolysis reactions with poor nucleophiles.

The reaction of the *threo*-tosylate with sodium azide in dimethylformamide resulted in the formation of the *erythro*-azide **13**. A minor side product was *trans*-2-phenyl-2-butene, which was formed by trans elimination of *p*-toluenesulfonic acid.

In the same manner the *erythro*-tosylate afforded the *threo*-azide **14** and small amounts of *cis*-2-phenyl-2-butene.

The crude azides (**13** and **14**) were not purified but were immediately reduced with lithium aluminum hydride to yield *erythro*- and *threo*-3-phenyl-2-butylamine (**2** and **1**), respectively. Amines **2** and **1** were passed through a Dowex 3 ion-exchange column, which had previously been charged with methanesulfonic acid to afford the corresponding *erythro*- and *threo*-methanesulfonate salts of **2** and **1**.

The *erythro*- and *threo*-3-phenyl-2-butylamine salts were reconverted to their corresponding free bases (**2** and **1**) and subjected to reductive alkylation according to the procedure of Engelhardt, *et al.*,[14] utilizing acetone as the alkylating agent and Adams platinum catalyst. The *erythro*- and *threo*-isopropylamines **6** and **5** were isolated as their hydrochloride salts.

The preparation of 1,2-disubstituted cyclohexane analogs of amphetamine as semirigid analogs served as model syntheses for the 2,3-disubstituted *trans*-decalin analogs.[15]

The synthesis of *cis*-2-phenylcyclohexylamine (**3**) was initiated with epoxidation of cyclohexene utilizing the procedure of Hibbert and Burt[16] as reported by Johnson, *et al.*,[17] to afford cyclohexene oxide (**15**).

Treatment of **15** with phenyllithium according to the procedure of Cook, *et al.*,[18] resulted in the formation of *trans*-2-phenylcyclohexanol (**16**). The trans alcohol **16** was converted to its tosylate **17** by treatment with *p*-toluenesulfonyl chloride in pyridine and to its mesylate **18** by treatment with methanesulfonyl chloride in pyridine. The trans stereochemistry was verified by the nmr spectrum. The nmr spectrum of **17** showed absorptions at δ 4.55 ($W_{1/2}$ = 20 Hz) indicative of an axial methine proton at C-1 and at δ 3.60 ($W_{1/2}$ = 20 Hz) indicative of an axial methine proton at C-2. The nmr spectrum of **18** showed absorptions at δ 4.62 ($W_{1/2}$ = 18 Hz) indicative of an axial methine proton at C-1 and at δ 3.65 also indicative of an axial methine proton at C-2.

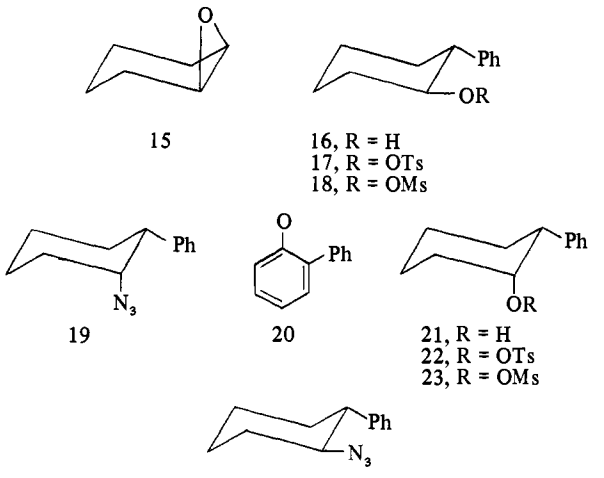
The reaction of the tosylate **17** with sodium azide in dimethylformamide resulted in the formation of *cis*-2-phenylcyclohexyl azide (**19**). This was immediately reduced with lithium aluminum hydride to yield *cis*-2-phenylcyclohexylamine **3** which was isolated both as the hydrochloride and the methanesulfonate salt. The nmr spectrum of **3** indicated cis stereochemistry with absorption at δ 3.25 ($W_{1/2}$ = 7 Hz) indicative of an equatorial conformation for the C-1 methine proton.

Compound **3** was converted to its isopropyl analog **7** and isolated as the hydrochloride salt according to the procedure discussed previously.

trans-2-Phenylcyclohexylamine (**4**) was prepared utilizing *o*-phenylphenol (**20**) as the starting material. The phenol **20** was reduced using a modification of the procedure reported by Price and Karabinos[19] to afford *cis*-2-phenylcyclohexanol (**21**).

The cis alcohol **21** was converted to the corresponding tosylate **22** and mesylate **23**. The nmr spectra of **22** and **23** both showed an absorption at δ 4.85 ($W_{1/2}$ = 7 Hz) indicative of a C-1 equatorial methine proton.

The reaction of the tosylate **22** with sodium azide in dimethylformamide resulted in the formation of *trans*-2-phenylcyclohexyl azide (**24**) which was immediately reduced with lithium aluminum hydride to yield the de-



15 16, R = H; 17, R = OTs; 18, R = OMs

19 20 21, R = H; 22, R = OTs; 23, R = OMs

24

sired *trans*-2-phenylcyclohexylamine (**4**) which was isolated both as the hydrochloride and the methanesulfonate salts. The trans stereochemistry was assigned from the nmr of the hydrochloride salt of **4** which showed absorption for the C-1 methine proton at δ 4.65 ($W_{1/2}$ = 2 Hz) and absorption for the C-2 methine proton at δ 2.85 ($W_{1/2}$ = 20 Hz) indicative of two axial protons.

trans-2-Phenylisopropylaminocyclohexane hydrochloride **8** was prepared from **4** according to the procedure discussed previously.

Biological Results. The approximate LD_{50} of amphetamine, the butane analogs (**1**, **2**, **5**, **6**), and the cyclohexane analogs (**3**, **4**, **7**, **8**) are listed in Table I. Male Swiss strain mice (20–30 g) were injected intravenously with either the methanesulfonate or hydrochloride salt of the given compounds and the LD_{50} was calculated by the method of Campbell and Richter.[20]

The behavioral effects of amphetamine, the butane analogs (**1**, **2**, **5**, **6**), and the cyclohexane analogs (**3**, **4**, **7**, **8**) are listed in Table II. The amine salts were injected intraperitoneally into male Swiss strain mice (20–30 g) and the gross behavior was determined by a trained observer.

The characteristic changes in behavior were obtained using the method of Campbell and Richter.[20] A dose of 25 mg/kg of amphetamine methanesulfonate administered intraperitoneally increased motor activity and caused salivation, lachrymation, mydriasis, piloerection, and erection of the tail (Straub phenomenon). Administration of the butanes and the cyclohexanes resulted in some of these behavioral changes; however, in no case were all of the behavioral patterns of amphetamine observed. The most interesting behavioral pattern was the change in motor activity which occurred from the minimal active dose up to the toxic dose upon intraperitoneal injection of these compounds. Amphetamine, the *erythro*-butanes, and the *cis*-cyclohexanes all increased motor activity, whereas the *threo*-butanes and the *trans*-cyclohexanes caused a decrease in motor activity.

The *erythro*-butanes and the *cis*-cyclohexanes are configurationally related as well as the *threo*-butanes and the *trans*-cyclohexanes. Therefore, these results suggest that the erythro configuration is required for an increase in motor activity by β-methylamphetamine, whereas the threo configuration caused a decrease in motor activity. Because these compounds are only semirigid, it cannot be concluded if a unique conformation is required for the increase in motor activity.

Table I. Toxicity of Phenethylamine-Like Compounds

Compound	Approximate LD_{50},[c] mg/kg
Amphetamine[b]	50
Butanes	
Erythro (2)[b]	46
Threo (1)[b]	55
Isopropylbutanes	
Erythro (6)[a]	38
Threo (5)[a]	28
Cyclohexanes	
Cis (3)[b]	9
Trans (4)[b]	28
Isopropylcyclohexanes	
Cis (7)[a]	23
Trans (8)[a]	23

[a]Hydrochloride salt. [b]Methanesulfonate salt. [c]See ref 20.

Table II. Behavioral Study of Phenethylamine-Like Compounds

Compound	Dose, mg/kg[c]	Duration, hr	MA[d]
Amphetamine[a]	25	2–6	+
Butanes			
Erythro (2)[a]	25	1–3	+
Threo (1)[a]	50	2	–
Isopropylbutanes			
Erhthro (6)[b]	25	2–3	+
Threo (5)[b]	25	2–3	–
Cyclohexanes			
Cis (3)[a]	25	1–2	+
Trans (4)[a]	25	1–2	–
Isopropylcyclohexanes			
Cis (7)[b]	12	1–2	+
Trans (8)[b]	25	1–2	–

[a]Methanesulfonate salt. [b]Hydrochloride salt. [c]Minimal dose required for changes in motor activity. [d](+) = increased motor activity; (–) = decreased motor activity.

Experimental Section‡

cis-2-Butene Oxide (9). *cis*-2-Butene oxide (9) was prepared according to the procedure of Pasto and Cumbo[10] using 85% *m*-chloroperbenzoic acid (130.6 g, 0.644 mol), *cis*-2-butene (Phillips Petroleum Co., 99.89% purity, 36.2 g, 0.644 mol), and dioxane as a solvent to yield 34.0 g (74%) of 9, bp 58.0–60.0° (745 mm) [lit.[10] 58.0–59.0° (748 mm)].

threo-3-Phenyl-2-butanol (11). To lump Li (765 mg, 0.110 g-atom), under a N_2 atmosphere, in 50 ml of anhydrous Et_2O was added C_6H_5Br (8.85 g, 0.055 mol) at such a rate as to maintain reflux. After addition was complete, the solution was stirred for an additional 2.5 hr and then cooled in an ice bath. *cis*-2-Butene oxide (9) (3.6 g, 0.050 mol) was added rapidly to the cooled solution. The ice bath was removed and the solution was refluxed for 2.5 hr and then stirred for 12 hr at 25°. The solution was quenched with H_2O and the aqueous layer was extracted several times with Et_2O. The combined Et_2O fractions were washed twice with saturated NaCl solution and dried ($MgSO_4$). The Et_2O was removed to afford 6.5 g (87%) of 11, bp 61° (0.15 mm) [lit.[11] 108° (10 mm)]. *Anal.* ($C_{10}H_{14}O$) C, H.

threo-3-Phenyl-2-butyl Tosylate. To *threo*-3-phenyl-2-butanol (11) (35.0 g 0.23 mol) in 70 ml of anhydrous C_5H_5N, cooled in an ice bath, was added *p*-TsCl (46.0 g, 0.24 mol). The solution was stirred for 48 hr at 25°. The mixture was then shaken with a cold excess of 2 *N* H_2SO_4, Et_2O, and hexane. The aqueous layer was extracted several times with a mixture of Et_2O–hexane. The combined organic fractions were washed with H_2O, 5% KOH solution, and saturated NaCl solution and dried ($MgSO_4$). The solvent was removed and the resulting solid was recrystallized (hexane–C_6H_6,

‡Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckmann IR-10 spectrophotometer and nmr data on Varian Associates Model A-60A and T-60 spectrometers (TMS). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on the F & M Model 185 C, H, N analyzer, University of Kansas, Lawrence, Kan. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

5:1) to afford 65.2 g (93%) of the desired compound, mp 47–48° (lit.[11] mp 47.6–48.2°).

erythro-3-Phenyl-2-butyl Azide (13). To *threo*-3-phenyl-2-butyl tosylate (55.0 g, 0.18 mol) in 1200 ml of DMF was added NaN_3 (35.0 g, 0.54 mol) in 50 ml of H_2O. The solution was stirred for 60 hr at 95°. H_2O was added to the solution and it was extracted several times with Et_2O. The combined Et_2O fractions were washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed to afford 33.5 g of crude azide 13, which was used without further purification.

erythro-3-Phenyl-2-butylamine (2). To a stirred suspension of $LiAlH_4$ (19.0 g 0.50 mol) in 500 ml of anhydrous Et_2O was added dropwise *erythro*-3-phenyl-2-butyl azide (13) (0.18 mol). The solution was stirred for 12 hr at 25°. Excess $LiAlH_4$ was decomposed with Na_2SO_4 wetted with 10% KOH solution. The inorganic salts were removed and the Et_2O layer was washed with saturated NaCl solution and dried ($MgSO_4$). The Et_2O was removed to afford 26.5 g of a crude oil. Distillation of the crude oil yielded several fractions which contained a mixture of the desired amine 2 and olefinic compounds. The pure amine 2 fraction had bp 100° (11 mm).

A 0.02 *M* solution of crude *erythro*-3-phenyl-2-butylamine (2) in MeOH was passed through an ion-exchange column containing a weakly basic resin (Dowex-3) charged with methanesulfonic acid. The MeOH was removed and the olefinic components were washed from the solid with hexane. Crystallization (C_6H_6) afforded 19.8 g (59%) of the methanesulfonate of 2 from 13, mp 154°. *Anal.* ($C_{11}H_{19}NO_3S$) C, H, N.

trans-2-Butene Oxide (10). *trans*-2-Butene oxide (10) was prepared according to the procedure of Pasto and Cumbo,[11] using 85% *m*-chloroperbenzoic acid (130.6 g, 0.644 mol), *trans*-2-butene (Phillips Petroleum Co., 99.63% purity, 36.2 g, 0.644 mol), and dioxane as a solvent to yield 30.6 g (67%) of 10, bp 52–53° (745 mm) [lit.[10] 52–53° (748 mm)].

erythro-3-Phenyl-2-butanol (12). The procedure utilized was the same as that for the preparation of 11. To lump Li (6.25 g, 0.90 g-atom), under a N_2 atmosphere, in 400 ml of anhydrous Et_2O was added C_6H_5Br (70.5 g, 0.450 mol). After the reaction was complete, *trans*-2-butene oxide (10) (30.0 g, 0.416 mol) was added to afford 31.0 g (50%) of 12, bp 57° (0.20 mm) [lit.[11] 105° (10 mm)].

erythro-3-Phenyl-2-butyl Tosylate. The procedure utilized was the same as in the tosylation of 11. To *erythro*-3-phenyl-2-butanol (12) (20.0 g, 0.133 mol) in 40 ml of anhydrous C_5H_5N, cooled in an ice bath, was added *p*-TsCl (27.0 g, 0.14 mol) to afford 38.6 g (97%) of an oil which failed to crystallize.

threo-3-Phenyl-2-butyl Azide (14). The procedure utilized was identical with that employed in the preparation of 13.

To *erythro*-3-phenyl-2-butyl tosylate (30.4 g, 0.10 mol) in 600 ml of DMF was added NaN_3 (19.5 g, 0.30 mol) in 40 ml of H_2O to afford 19.5 g of crude azide 14, which was used without further purification.

threo-3-Phenyl-2-butylamine (1). The procedure for the preparation of 1 and its methanesulfonate salt was essentially the same as that used for the preparation of 2 and its methanesulfonate salt.

To a stirred suspension of $LiAlH_4$ (11.0 g, 0.30 mol) in 250 ml of anhydrous Et_2O was added dropwise *threo*-3-phenyl-2-butyl azide (14) (0.10 mol) to afford 14.0 g of a crude oil. Distillation of the crude oil yielded several fractions which contained a mixture of the desired amine 1 and olefinic compounds. Pure amine 1 had fraction bp 110° (17 mm).

A 0.02 *M* solution of crude *threo*-3-phenyl-2-butylamine (1) in MeOH was passed through an ion-exchange column containing a weakly basic resin (Dowex-3) charged with methanesulfonic acid to afford 14.2 g (58%) of the methanesulfonate salt of 1 from 14, mp 100°. *Anal.* ($C_{11}H_{19}NO_3S$) C, H, N.

Cyclohexene Oxide (15). The procedure used was essentially that of Hibbert and Burt,[16] as reported by Johnson, *et al.*[17] To a cold solution (0°) of 87% *m*-chloroperbenzoic acid (31.7 g, 0.16 mol) in 300 ml of $CHCl_3$ was added cautiously cyclohexene (12.5 g, 0.15 mol) in 50 ml of $CHCl_3$. *m*-Chlorobenzoic acid precipitated out of the solution. The solution was placed in the refrigerator for 12 hr and then extracted with 5% NaOH solution and H_2O and dried ($MgSO_4$). The solvent was removed and the resulting liquid was distilled to afford 14.7 g of 15, bp 100–130°. Osterberg[21] reported the following boiling points for cyclohexene oxide (15), bp 100–125° (contaminated with H_2O) and bp 124–134° (anhydrous).

trans-2-Phenylcyclohexanol (16). *trans*-2-Phenylcyclohexanol (16) was prepared according to the procedure of Cook, *et al.*,[18] using lump Li (10.7 g, 1.54 g-atoms), C_6H_5Br (112.2 g, 0.715 mol), cyclohexene oxide (15) (74.5 g, 0.759 mol), and anhydrous Et_2O as a solvent to yield 41.4 g (31%) of 16, bp 100–110° (1 mm) [lit.[18] 153–154° (16 mm)].

trans-2-Phenylcyclohexyl Tosylate (17). To *trans*-2-phenylcyclohexanol (16) (4.4 g, 0.025 mol) in 80 ml of anhydrous C_5H_5N, cooled in an ice bath, was added *p*-TsCl (9.95 g, 0.050 mol). The solution was stirred for 6 hr and then placed in the refrigerator for 36 hr. This solution was poured into 300 ml of ice–H_2O. The precipitate was crystallized (Me_2CO) to afford 6.7 g (87.5%) of 17: mp 144° dec (lit.[22] 131–132° from EtOH); nmr ($CDCl_3$) δ 7.40–6.90 (m, 9 H, aromatic), 4.55 (m, 1 H, $W_{1/2}$ = 20 Hz, C-1 CH), 2.35 (s, 3 H, aryl CH_3). *Anal.* ($C_{19}H_{22}O_3S$) C, H.

trans-2-Phenylcyclohexyl Mesylate (18). To *trans*-2-phenylcyclohexanol (16) (33.0 g, 0.19 mol) in 250 ml of anhydrous C_5H_5N, cooled in an ice bath, was added methanesulfonyl chloride (43.7 g, 0.38 mol). The solution was stirred for 1.5 hr and then placed in the refrigerator for 12 hr. This solution was poured into 600 ml of ice–H_2O. The precipitate was crystallized (Me_2CO) to afford 38.5 g (81%) of 18: mp 113°; nmr ($CDCl_3$) δ 7.35 (s, 5 H, aromatic), 4.62 (m, 1 H, $W_{1/2}$ = 18 Hz, C-1 CH), 2.10 (s, 3 H, CH_3SO_3). *Anal.* ($C_{13}H_{18}O_3S$) C, H.

cis-2-Phenylcyclohexyl Azide (19). To *trans*-2-phenylcyclohexyl tosylate (17) (6.0 g, 0.018 mol) in 250 ml of DMF was added NaN_3 (3.9 g, 0.06 mol) in 15 ml of H_2O. The solution was stirred for 48 hr at 95°. H_2O was added to the solution and it was extracted several times with Et_2O. The combined Et_2O fractions were washed with saturated NaCl solution and H_2O and dried ($MgSO_4$). The solvent was removed to afford 3.6 g of crude azide 19 which was used without further purification.

cis-2-Phenylcyclohexylamine (3). To a stirred suspension of $LiAlH_4$ (3.0 g, 0.079 mol) in 130 ml of anhydrous Et_2O was added dropwise *cis*-2-phenylcyclohexyl azide (19) (0.18 mol) in 30 ml of anhydrous Et_2O. The solution was stirred for 4 hr after the addition was complete. Excess $LiAlH_4$ was decomposed with "wet" Et_2O followed by H_2O. The inorganic salts were removed and the Et_2O layer was washed with saturated NaCl solution and H_2O and dried ($MgSO_4$). The solvent was removed to afford 2.6 g (90%) of 3: nmr ($CDCl_3$) 3.25 (m, 1 H, $W_{1/2}$ = 7 Hz, C-1 CH).

The hydrochloride salt of 3 was prepared from the free base. The solid was recrystallized (MeOH–H_2O): mp 209–210° (lit.[23] 205–207°). *Anal.* ($C_{12}H_{18}ClN$) C, H, N.

The methanesulfonate salt of 3 was prepared from the free base. The solid was recrystallized (C_6H_6), mp 180°.

cis-2-Phenylcyclohexanol (12). The procedure used by Price and Karabinos[19] was modified by using T-1 Raney Ni as prepared by Dominquez, *et al.*[24] *o*-Phenylphenol (20) (34.0 g, 0.20 mol) was dissolved in 34 ml of absolute EtOH containing 1 ml of 20% NaOH solution. The mixture was subjected to hydrogenation (60 psi, 25°) for 72 hr. The residue was dissolved in Et_2O and washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed and the resulting liquid was distilled affording 25.5 g (43%) of 21, bp 129–131° (13 mm) [lit.[19] 140–141° (16 mm)].

cis-2-Phenylcyclohexyl Tosylate (22). To *cis*-2-phenylcyclohexanol (21) (20.0 g, 0.113 mol) in 40 ml of anhydrous C_5H_5N, cooled in an ice bath, was added *p*-TsCl (23.0 g, 0.120 mol). The solution was stirred for 48 hr at 25° and then poured into a cold solution of 2 *N* H_2SO_4. The aqueous solution was extracted several times with $CHCl_3$ and the combined $CHCl_3$ fractions were washed with H_2O, 5% KOH solution, and saturated NaCl solution and dried ($MgSO_4$). The solvent was removed and the solid was recrystallized (hexane–C_6H_6) to afford 20.7 g (60%) of 22: mp 132° dec (lit.[22] 103.5–104°, from EtOH); nmr ($CDCl_3$) δ 8.45–6.85 (m, 9 H, arom), 4.85 (m, 1 H, $W_{1/2}$ = 7 Hz, C-1 CH), 2.40 (s, 3 H, aryl CH_3). *Anal.* ($C_{19}H_{22}O_3S$) C, H.

cis-2-Phenylcyclohexyl Mesylate (23). To *cis*-2-phenylcyclohexanol (21) (3.85 g, 0.022 mol) in 50 ml of anhydrous C_5H_5N, cooled in an ice bath, was added methanesulfonyl chloride (5.02 g, 0.044 mol). The solution was stirred for 1 hr and then placed in the refrigerator for 12 hr. This solution was poured into 200 ml of ice–H_2O, and the solid obtained was recrystallized (Me_2CO) to afford 4.1 g (74%) of 23: mp 90°; nmr ($CDCl_3$) δ 7.30 (s, 5 H, arom), 4.85 (m, 1 H, $W_{1/2}$ = 7 Hz, C-1 CH), 2.85 (m, 1 H, C-2 CH), 2.15 (s, 3 H, CH_3SO_3). *Anal.* ($C_{13}H_{18}O_3S$) C, H.

trans-2-Phenylcyclohexyl Azide (24). The procedure used was identical with that used in the preparation of 19.

To *cis*-2-phenylcyclohexyl tosylate (22) (20.7 g, 0.063 mol) in 375 ml of DMF was added NaN_3 (12.3 g, 0.19 mol) in 25 ml of H_2O to afford 19.0 g of crude azide 24 which was used without further purification.

trans-2-Phenylcyclohexylamine (4). The procedure used was

identical with that used in the preparation of 3.

To a stirred suspension of $LiAlH_4$ (3.8 g, 0.105 mol) in 125 ml of anhydrous Et_2O was added dropwise *trans*-2-phenylcyclohexyl azide (24) (0.063 mol, theoretically) in 50 ml of anhydrous Et_2O to afford 10.1 g (83%) of 4.

The hydrochloride salt of 4 was prepared from the free base. The solid was recrystallized (C_6H_6), mp 238° dec (lit.[23] mp 249–251°).

The methanesulfonate salt of 4 was prepared from the free base. The solid was recrystallized (C_6H_6), mp 156°. *Anal.* ($C_{13}H_{21}NO_3$) C, H, N.

General Procedure for Preparation of Isopropyl Analogs. The amine salt was converted to the free amine by the use of a strong base ion-exchange column (Amberlite IRA-400) or by adding the amine salt to a saturated NH_3–$CHCl_3$ solution, filtering the ammonium salt, and evaporating the solvent to yield the free amine. The free amine was dissolved in absolute EtOH containing 5% MeOH and to this solution was added a 4 *M* excess amount of Me_2CO. The solution was subjected to hydrogenation over Adams platinum catalyst at 32 psi at 25° for 12 hr. The catalyst and the solvent were removed to afford the isopropyl analog as the free amine, which was dissolved in Et_2O. The hydrochloride salt was prepared by addition of saturated HCl-Et_2O solution to the ethereal solution. The salt was removed by filtration and recrystallized from the appropriate solvent.

erythro-2-Isopropylamino-3-phenylbutane Hydrochloride (6). This compound was recrystallized from $CHCl_3$–hexane, mp 181.5–182.5°. *Anal.* ($C_{13}H_{22}ClN$) C, H, N.

threo-2-Isopropylamine-3-phenylbutane Hydrochloride (5). This compound was recrystallized from MeOH–hexane, mp 228°. *Anal.* ($C_{13}H_{22}ClN$) C, H, N.

cis-2-Phenylisopropylaminocyclohexane Hydrochloride (7). This compound was recrystallized from C_6H_6, mp 228°. *Anal.* ($C_{15}H_{24}ClN$) C, H, N.

trans-2-Phenylisopropylaminocyclohexane Hydrochloride (8). This compound was recrystallized from C_6H_6, mp 213–215°. *Anal.* ($C_{15}H_{24}ClN$) C, H, N.

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References

(1) E. E. Smissman, W. L. Nelson, J. B. LaPidus, and J. L. Day, *J. Med. Chem.*, 9, 458 (1966).
(2) E. E. Smissman and W. H. Gastrock, *ibid.*, 11, 860 (1968).
(3) E. E. Smissman and G. S. Chappell, *ibid.*, 12, 429 (1969).
(4) E. E. Smissman and G. S. Chappell, *ibid.*, 12, 432 (1969).
(5) E. E. Smissman and R. T. Borchardt, *ibid.*, 14, 377 (1971).
(6) E. E. Smissman and R. T. Borchardt, *ibid.*, 14, 383 (1971).
(7) E. E. Smissman and S. J. Vickers, *ibid.*, 13, 1224 (1970).
(8) E. E. Smissman and S. El-Antably, *ibid.*, 14, 30 (1971).
(9) J. H. Biel, *Int. Symp. Amphetamines Relat. Compounds, Proc.*, 3 (1970).
(10) D. J. Pasto and C. C. Cumbo, *J. Org. Chem.*, 30, 1271 (1965).
(11) D. J. Cram, *J. Amer. Chem. Soc.*, 71, 3863 (1949).
(12) D. J. Cram, *ibid.*, 74, 2129 (1952).
(13) D. J. Cram and J. A. Thompson, *ibid.*, 89, 6766 (1967).
(14) E. L. Engelhardt, F. S. Crossley, and J. M. Sprague, *ibid.*, 72, 2718 (1950).
(15) E. E. Smissman and T. L. Pazdernik, *J. Med. Chem.*, 16, 000 (1973).
(16) H. H. Hibbert and P. Burt, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 494.
(17) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. D. Dreger, and W. N. Hubbard, *J. Amer. Chem. Soc.*, 83, 606 (1961).
(18) J. W. Cook, G. L. Hewett, and C. A. Lawrence, *J. Chem. Soc.*, 71 (1936).
(19) C. C. Price and J. V. Karabinos, *J. Amer. Chem. Soc.*, 62, 1159 (1940).
(20) D. E. S. Campbell and W. Richter, *Acta Pharmacol. Toxicol.*, 25, 345 (1967).
(21) A. E. Osterberg, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 494.
(22) S. A. Roman and W. D. Closson, *J. Amer. Chem. Soc.*, 91, 1701 (1969).
(23) S. J. Cristol and F. R. Stermitz, *ibid.*, 82, 4692 (1960).
(24) Y. A. Dominquez, I. C. Lopez, and F. Franco, *J. Org. Chem.*, 26, 1625 (1961).

A Conformational Study of Phenethylamine Receptor Sites. 2. Synthesis of *dl*-2-Amino-3-phenyl-*trans*-decalins and *dl*-2-Isopropylamino-3-phenyl-*trans*-decalins

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The syntheses of the four possible *dl*-2-amino-3-phenyl-*trans*decalin isomers, **1**–**4**, and the four possible *dl*-2-isopropylamino-3-phenyl-*trans*-decalin isomers, **5**–**8**, are described. The results of the toxicity and behavioral studies are described.

In a previous report from these laboratories it was shown that when the phenethylamine structure was incorporated into a semirigid system the erythro configuration appeared to be required for an increase in motor activity similar to that which is found with the parent compound amphetamine.[1] Since a marked difference in activity with a change in configuration was observed, an investigation of rigid analogs which represent various fixed conformations of the *threo*- and *erythro*-β-methylamphetamines was undertaken.

The synthesis of the four racemic isomers of *dl*-2-amino-3-phenyl-*trans*-decalin, **1**–**4**, afford two compounds with the threo configuration (**1** and **4**) and two compounds with the erythro configuration (**2** and **3**). The *N*-isopropyl-β-methylamphetamine analogs, **5**–**8**, were prepared since the substitution of an isopropyl group in the parent compound, amphetamine, results in greater specificity for anorexic effect and the hypothesis is offered that different conformations may be required at the various effector or metabolic sites.

The synthesis of 2(e)-amino-3(e)-phenyl-*trans*-decalin (**1**) and 2(a)-amino-3(e)-phenyl-*trans*-decalin (**2**) was initiated with the oxidation of commercially available *trans*-2-decalol (**9**) to *trans*-2-decalone (**10**) utilizing Jones reagent according to the procedure of Ramsey.‡

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‡A. Ramsey, Ph.D. Thesis, University of Kansas, 1968.