was added, and the mixture was left at 5° overnight. Work-up resulted in a brown oil: 8.0 g (87%); ir 2990, 2950, 2850 (CH), 2220 (C≡N), 1595, 1550, 1490 cm^{-1} (aromatic). An estimated 5% of the enol 1 could be detected in the ir spectrum.

2,4-Diamino-5-(*p*-chlorophenyl)-6-pyrimidinyl Methyl Ketone Dimethyl Acetal (4). To a solution of 6.9 g (0.3 mol) of sodium metal in 100 ml of EtOH there was added 8.0 g (0.028 mol) of crude 2 in 50 ml of EtOH, followed by 27.0 g of guanidine·$2HNO_3$, and the resulting mixture was stirred under reflux for 2 h. EtOH was removed in vacuo and H_2O was added until there appeared a crystalline solid: 8.0 g; mp 235–245°. Recrystallization from $CHCl_3$–MeOH gave the analytical sample (6.0 g, 70%).

2,4-Diamino-5-(*p*-chlorophenyl)-6-pyrimidinyl Methyl Ketone (6). Compound 4 (5 g, 0.016 mol) was dissolved in 200 ml of MeOH and 20 ml of concentrated HCl and the whole mixture was refluxed for 2.0 h. Concentration of the methanolic solution to one-third volume caused precipitation of the hydrochloride salt, which was filtered (4.8 g), dissolved in warm water, and precipitated with concentrated NH_4OH, giving the desired ketone (4.0 g, 95%), mp 200–204°. Recrystallization from $CHCl_3$–MeOH gave the analytical sample.

***dl*-2,4-Diamino-5-(*p*-chlorophenyl)-α-methyl-6-pyrimidinemethanol (7).** Compound 6 was reduced in MeOH by $NaBH_4$, yielding 88% of the respective alcohol.

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Conformationally Rigid Amphetamine Analogs as Inhibitors of Monoamine Uptake by Brain Synaptosomes

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Four 3-phenyl-2-amino-*trans*-decalin isomers were synthesized in order to obtain derivatives of phenylethylamine with a rigid conformation between the phenyl ring and the amino function. The stereoisomers were tested as inhibitors of catecholamine uptake by rat brain synaptosomes, and their potency was compared with that of amphetamine. The most potent inhibitor of catecholamine uptake was the diaxial 2(a)-amino-3(a)-phenyl-*trans*-decalin, which was one-fourth to one-third as potent as (±)-amphetamine. As a dopamine uptake inhibitor in the striatum, this compound was competitive. The results differ from those obtained earlier with similar analogs with a norepinephrine moiety incorporated into the decalin structure, since a gauche derivative [2(a)-amino-3(e)-3,4-dihydroxyphenyl-3-*trans*-decalol] was then the most potent and over 20 times as potent as the diaxial anti derivative. It remains to be seen whether this indicates that the mode of binding of phenylethylamines is different from that of catecholamines.

In recent work at these laboratories 3-catechol derivatives of 2-amino-*trans*-3-decalol were studied as inhibitors of dopamine uptake.[1] In these compounds the structure of sterically rigid norepinephrine can be found. Four racemic isomers were utilized: in one of them the relation between the catechol ring and the amino group was anti; in the three others it was gauche. One of the gauche derivatives, (±)-2(a)-amino-3(e)-3,4-dihydroxyphenyl-3-*trans*-decalol, was by far the most potent dopamine uptake inhibitor, and the potency was one-half that of (−)-norepinephrine. The result was interpreted as suggesting that a gauche conformation is preferable for uptake inhibition and that the uptake site might require the substrate in this conformation as well.

The present experiments extended the study to amphetamine-like *trans*-decalin derivatives. These compounds have been tested previously as inhibitors of 5-hydroxytryptamine and histamine uptake by rabbit blood platelets, but no clear structural correlation was found in those experiments.[2,3]

Results and Discussion

Active Uptake of Dopamine and Norepinephrine. The uptake characteristics of dopamine agreed closely with those observed previously.[1] A tissue–medium ratio of 90.0 ± 11.5 (SD) was obtained in 5 min when the substrate concentration was 10^{-7} M (the ratio was calculated for the original wet weight of striatal tissue and would thus be much higher for the synaptosomal fraction actually used). The uptake was saturable, and the kinetic constants were $K_m = 8.8 \times 10^{-8}$ M and $V_{max} = 11.2$ nmol/g/5 min.

Norepinephrine uptake in the hypothalamic homogenate was somewhat more active than in cortical homogenates in identical experimental conditions,[4] which is in agreement with the results of Snyder and Coyle.[5] A tissue–medium ratio of 6.4 ± 1.0 (SD) was obtained in 5 min at a substrate concentration of 10^{-8} M.

Inhibition of Uptake. All four decalin derivatives were less potent inhibitors of norepinephrine and dopamine uptake than (±)-amphetamine, and the most potent derivative was the diaxial anti isomer (Table I, Figure 1). These results differ clearly from those obtained with the catechol derivatives, since the anti isomer of the catechol derivatives was significantly less potent than one of the gauche isomers, 2(a)-amino-3(e)-3,4-dihydroxyphenyl-3-*trans*-decalol.[1] The difference between dopamine uptake and norepinephrine uptake was also smaller than in experiments with catechol derivatives (cf. Figure 1).

NE	DA	NE	DA
100	100	100	100
30	25	4.4	2.3
1.1	8	8.9	50
2.2	4.8	0.03	1.1
3.6	14	2.0	5.7

Figure 1. Relative potency of (±)-amphetamine (=100) and the respective decalin analogs on norepinephrine uptake in the hypothalamic and dopamine uptake in the striatal synaptosomes (two left columns, respectively). For comparison, previous data on norepinephrine and respective decalol analogs are given (two right columns, ref 6 and 1, respectively).

Table I. IC_{50} Values of Compounds Studied as Norepinephrine (NE) and Dopamine (DA) Uptake Inhibitors[a]

Compound	NE, hypothalamus, M	DA, striatum, M
(±)-Amphetamine	2×10^{-7}	9.6×10^{-7}
(±)-2(a)-Amino-3(a)-phenyl-*trans*-decalin (1)	6.6×10^{-7}	3.8×10^{-6}
(±)-2(a)-Amino-3(e)-phenyl-*trans*-decalin (2)	1.8×10^{-5}	1.2×10^{-5}
(±)-2(e)-Amino-3(a)-phenyl-*trans*-decalin (3)	9×10^{-6}	2×10^{-5}
(±)-2(e)-Amino-3(e)-phenyl-*trans*-decalin (4)	5.5×10^{-6}	7×10^{-6}

[a] The synaptosomal preparations were incubated for 5 min in Krebs-Henseleit bicarbonate buffer, pH 7.4, containing the radioactive substrate (10^{-8} M NE or 10^{-7} M DA), the inhibitor to be studied, 0.2 mg/ml of ascorbic acid, and 1.25×10^{-5} M nialamide. At least three concentrations of each inhibitor were tested for the IC_{50} estimations, and two to six duplicate experiments were performed for each concentration (at least six for the concentration closest to IC_{50}).

Kinetics of Uptake. The double-reciprocal plots indicate that the K_m of dopamine uptake was increased in the presence of the inhibitor (the anti derivative), and there was no significant change in the V_{max}. This agrees with the competitive type of inhibition (Figure 2).

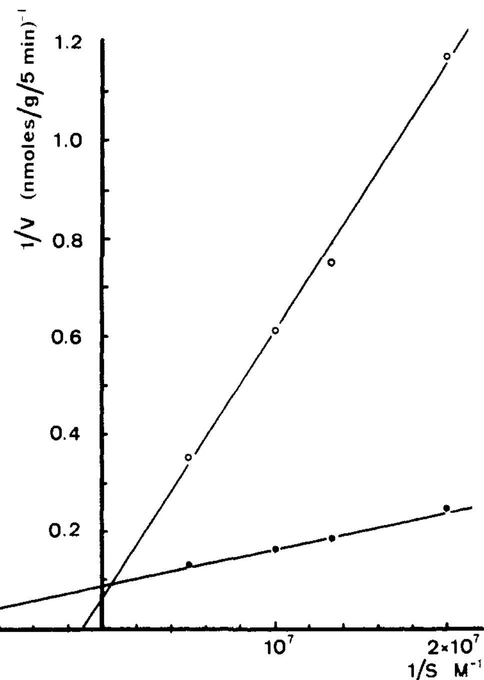

Figure 2. Double-reciprocal plot of dopamine uptake by striatal homogenate. The plot with the inhibitor 2(a)-amino-3(a)-phenyl-*trans*-decalin (10^{-5} M, open circles) shows increased K_m and unchanged V_{max}, which agrees with the competitive type of inhibition.

Conclusions

The most favorable conformation for inhibitory potency among decalin derivatives of the amphetamine type seems to be different from that among decalin derivatives containing a norepinephrine moiety. The most potent isomer of amphetamine-like compounds had the amino function and the phenyl ring in the anti configuration, whereas that of norepinephrine-like compounds had the amino function and the catechol ring in gauche configuration. Some uncertainty, of course, is caused by the fact that these compounds are much bulkier and more lipophilic than the parent compounds. It remains to be seen whether the differences of potencies also indicate that the mode of binding to the transport sites of the phenylethylamines is different from that of the catecholamines. This is not unlikely, because there may be two sites for binding aromatic rings at the receptor of the amine transport mechanism (cf. ref 7). This would offer a simple

explanation of the extraordinarily high affinity of various tricyclic and related compounds which have two aromatic rings at a certain angle to one another.

Experimental Section

Derivatives 1–4 were synthetized according to Smissman and Pazdernik,[8] and both they and (±)-amphetamine were tested as inhibitors of norepinephrine uptake in rat hypothalamic homogenates containing synaptosomes and as inhibitors of dopamine uptake in striatal homogenates. Details of the procedure have been published previously.[1] The brain tissue was homogenized and centrifuged at low speed to remove debris; then the supernatant which contained synaptosomes was incubated for 5 min in Krebs–Henseleit buffer at pH 7.4 with 10^{-8} M [^{3}H]norepinephrine (New England Nuclear, 6.5 Ci/mmol) or 10^{-7} M [^{3}H]dopamine (The Radiochemical Centre, 500 mCi/mmol), various concentrations of the inhibitor or solvent, 0.2 mg/ml of ascorbic acid, and 1.25×10^{-5} M nialamide. After incubation the particulate materials were separated with a membrane filter (Schleicher & Schüll, cellulose nitrate filter, 0.45-μm pore size) and washed with saline. The filter was transferred to a counting vial and the radioactivity accumulated in the tissue was measured by scintillation counting. The inhibition of uptake was calculated as a percentage of the uptake in control samples without an inhibitor. The percentage inhibition was transferred to probit, and the IC_{50} (concentration inhibiting 50% of uptake) was calculated by using semilogarithmic paper. The data obtained with different substrate concentrations were treated for use in double-reciprocal kinetic plots as previously described.[1] Student's *t* test was used to calculate the significance of the differences between two means.

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Partition Coefficients and Surface Areas of Some Alkylbenzenes

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The experimentally measured log *P* values (logarithms of partition coefficients) of a number of alkylbenzenes are shown to be quantitatively related to the hydrocarbon surface area HSA of the molecule by $\pi = 0.0275 \times \text{HSA} - 0.863$ (correlation coefficient = 0.996, standard deviation = 0.071). The use of surface area as a correlating parameter eliminates the need for correction factors to account for branching, cyclization, ring fusion, and "backfolding". Furthermore, surface area calculations provide a conceptual basis for understanding how conformation can effect partitioning.

The partition coefficient of a drug is commonly recognized as a key parameter in determining its biological activity. Unfortunately, this parameter cannot usually be determined for the appropriate biological system and we must settle for data obtained by some in vitro partitioning experiment. Octanol–water is by far the most frequently used system for such experiments and has served as an adequate model for correlation with biological data.

Since the pioneering work of Collander[1] there has been a great deal of interest in correlating partition coefficients or π values with chemical structure. The group contribution approach using the substituent constants compiled by Hansch[2] and Leo et al.[3] is probably the most accepted means of estimating log *P* values for organic compounds in the octanol–water system. While this approach is generally quite good, it cannot be consistently relied upon to give accurate values of log *P* especially for cyclic, condensed, or multiply branched or for coiled or folded molecules.

It is well known that an extended hydrocarbon will invariably have a higher partition coefficient than its branched isomers. In most cases, the differences can be accounted for by simple correction factors but in complex molecules this is often difficult. In any case, there is no clear-cut explanation for the effects due to isomerism or other structural features on partition coefficients.

Table I. Log *P* (Octanol–Water) and Total Surface Area (TSA) of Alkylbenzenes

Compound	Log *P* exptl	Log *P* calcd from eq 1	TSA, Å^2
Benzene	2.13	2.15	109.5
Toluene	2.69	2.62	126.5
Ethylbenzene	3.15	3.13	144.9
Propylbenzene	3.68	3.63	163.0
Isopropylbenzene	3.66	3.64	163.4
Indan	3.33	3.30	151.1
Tetralin	3.52[a]	3.63	163.0
tert-Butylbenzene	4.11	4.01	176.8
Cyclopentylbenzene	4.27[a]	4.20	183.7
Cyclohexylbenzene	4.64[a]	4.58	197.4
1-Adamantylbenzene	5.43[b]	5.53	232.0
o-Xylene	3.12	3.18	146.8
m-Xylene	3.20	3.28	150.3
p-Xylene	3.15	3.28	150.3

[a] Based on substituted phenoxyacetic acid data (see ref 6). [b] Based on adamantyl alcohol data (see ref 6).

We propose that the differences observed in the partition coefficients of aliphatic and aromatic compounds having the same number of carbon atoms can be fully explained on the basis of differences in the surface areas