cis-3a,4,5,9b-Tetrahydrobenzo[e]isoindoline Hydrochloride (6a). The above salt, 5 g in 100 ml of EtOH, was hydrogenated with 0.2 g of PtO_2 and H_2 at 4.2 kg/cm^2 until uptake ceased. The catalyst and solvent were removed and the product was crystallized several times from EtOH: yield 4.2 g; mp 228–230°. *Anal.* ($C_{12}H_{15}N$·HCl) C, H.

cis-2-Methyl-3a,4,5,9b-tetrahydrobenzo[e]isoindoline (6b). Method A. The base from 3 g of the **6a** salt above, 14.5 ml of 90% HCOOH, and 9.5 ml of 37% HCHO were heated under reflux in an oil bath for 4 hr. The mixture was cooled, 10 ml of 10% HCl was added, and it was distilled to dryness. Excess dilute NaOH was added to the residue and the product was extracted with ether, dried over K_2CO_3, and distilled: bp 130–132° (4 mm). *Anal.* ($C_{13}H_{17}N$) C, H, N.

6b hydrochloride was crystallized from MeCN: mp 175–177°. *Anal.* ($C_{13}H_{18}NCl$) C, H, N.

Method B. *cis*-1,2-Dihydronaphthalene-1,2-dicarboxylic anhydride,[4] 15 g in 200 ml of EtOAc, was hydrogenated with 2 g of 5% Pd/C and H_2 at 4.2 kg/cm^2. This gave 11 g of the *cis*-1,2,3,4-tetrahydro anhydride,[5] mp 61–63°. Anhydrous $MeNH_2$ was passed through a solution of 10 g of this anhydride in 200 ml of xylene while the temperature was raised slowly to 100°. The mixture was refluxed with removal of H_2O for 2 hr and evaporated *in vacuo* and the residue was crystallized from ether, yielding 7 g of *cis-N*-methyl-1,2,3,4-tetrahydronaphthalene-1,2-dicarboximide, mp 79–80°. *Anal.* ($C_{13}H_{13}NO_2$) C, H, N. This material, refluxed for 12 hr with 4 g of $LiAlH_4$ in 500 ml of ether and worked up as described for **7**, gave 4.2 g of amine identical with that obtained by method A (ir and nmr spectra, melting point, and mixture melting pont of the hydrochlorides).

cis-2-Acetyl-3a,4,5,9b-tetrahydrobenzo[e]isoindoline (6c). The base **6a** with $(CH_3CO)_2O$ in the usual manner gave crystals, mp 76–78°, from ether. *Anal.* ($C_{14}H_{17}NO$) C, H, N.

cis-2-Ethyl-3a,4,5,9b-tetrahydrobenzo[e]isoindoline Hydrochloride (6d). The reduction of 5 g of **6c** with 2 g of $LiAlH_4$ in 200 ml of refluxing ether for 7 hr gave the amine which with dry HCl in ether yielded 3.8 g of this salt, mp 179–180° from MeCN. *Anal.* ($C_{14}H_{19}N$·HCl) C, H, N.

3-Cyclopropylmethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (11). A solution of 17.3 g (0.1 mol) of **7** in 500 ml of benzene was stirred and 5.3 g (0.05 mol) of cyclopropylcarbonyl chloride in 50 ml of benzene was added. After 0.5 hr the salt was filtered and the benzene was washed with dilute HCl, dilute NaOH, and H_2O. Distillation of the solvent left a viscous residue of the amide which was reduced to **11** as described for **6d**.

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Correlation of Psychotomimetic Activity of Phenethylamines and Amphetamines with 1-Octanol–Water Partition Coefficients

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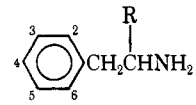
In an attempt to relate the hallucinogenic potencies in man of some biologically important amphetamines and phenethylamines, the 1-octanol–water partition coefficients for 11 amphetamines were determined. Using these values and published Hansch π constants, the log P for 17 additional amines was estimated. It was found that lipophilicity, as measured by the log of the partition coefficient, may be a significant determinant of the level of hallucinogenic potency. The study also suggests that an ideal log P value for psychotomimetic activity in man may be from 2.89 to 3.72.

The persisting major problem of research with psychotomimetic agents is the relationship of activity to physicochemical and structural properties of the active drugs. For the psychotomimetic amines, correlations have been attempted between activity and (1) the energy of the highest occupied molecular orbital;[1,2] (2) ultraviolet absorption maxima and molar absorptivity;[3] (3) degree of fluorescence;[4] and (4) stability of molecular complexes with dinitrobenzene.[5] Several correlations have been suggested between activity and conformation[6-8] and between activity and ability to stimulate various physiological receptors.[9,10] Numerous other studies have focused on relating metabolism, substitution patterns, and other chemical or metabolic factors to psychotomimetic activity.

The relationship between lipophilicity and activity has not been established. While drug action ultimately may be related to chemical or electronic factors, distribution and transport to the receptor may also be important in assigning relative contributions to the various components of drug action *in vivo*. We decided to study 1-octanol–water partition coefficients of psychotomimetic amines and examine whether a relationship exists between this parameter and activity.

Method. Partition coefficients were determined in the 1-octanol–water system according to published procedures.[11] The aqueous phase was buffered to pH 7.4 using phosphate buffer and the partitioning was done at room temperature. Under these conditions the amines are partially ionized. The partition coefficients are reported as that of the neutral species with correction for ionization being made according to Albert.[12] The pK_a of 2,5-dimethoxyamphetamine, which is reported to be 9.60,[13] was used in the correction. This is identical with the pK_a reported for mescaline.[14] The additive nature of log P[15] was used to estimate this parameter for those agents for which it was not available experimentally.

Table I. Structure and Activity Data for Psychotomimetic Amines



	2	3	4	5	6	R	Log P	Log act. Obsd	Log act. Calcd	[Δ log act.]
1		OCH_3	OCH_3	OCH_3		H	1.18[a]	0.00	−0.15	0.15
2		OCH_3	OCH_3	OCH_3		CH_3	1.48[b]	0.34	0.39	0.05
3	OCH_3		OCH_3			CH_3	1.75[b]	0.70	0.81	0.11
4			OCH_3			CH_3	1.77[b]	0.70	0.83	0.13
5	OCH_3			OCH_3		CH_3	1.88[b]	0.90	0.98	0.08
6	OCH_3		OCH_3		OCH_3	CH_3	1.57[b]	1.00	0.54	0.46
7	OCH_3		OCH_3	OCH_3		CH_3	1.74[b]	1.23	0.79	0.44
8	OCH_3		CH_3	OCH_3		CH_3	2.08[b]	1.90	1.21	0.69
9	OCH_3		n-C_3H_7	OCH_3		CH_3	3.31[c]	1.90	1.76	0.14
10	OCH_3		n-C_4H_9	OCH_3		CH_3	3.81[d]	1.56	1.55	0.01
11	OCH_3		C_2H_5	OCH_3		CH_3	2.81[b]	2.00	1.72	0.28
12	OCH_3		Br	OCH_3		CH_3	2.58[b]	2.60	1.62	0.98
13		$-OCH_2O-$				CH_3	1.68[e]	0.48	0.71	0.23
14		OCH_3	$-OCH_2O-$			CH_3	1.80[f]	0.43	0.87	0.44
15	OCH_3		$-OCH_2O-$			CH_3	2.42[g]	1.08	1.52	0.44
16	OCH_3	$-OCH_2O-$				CH_3	2.04[h]	1.00	1.17	0.17
17	$-OCH_2O-$		OCH_3			CH_3	1.72[i]	0.48	0.76	0.28
18	OCH_3	$-OCH_2O-$		OCH_3		CH_3	2.16[j]	1.08	1.29	0.21
19	OCH_3	OCH_3	$-OCH_2O-$			CH_3	2.54[k]	0.70	1.59	0.89
20	OCH_3		OCH_3	OCH_3		H	1.44[l]	0.00	0.32	0.32
21		$-OCH_2O-$				H	1.38[m]	0.00	0.22	0.22
22	OCH_3	OCH_3		OCH_3		CH_3	1.61[n]	0.60	0.60	0.00
23	OCH_3	OCH_3	OCH_3	OCH_3		CH_3	1.48[o]	0.78	0.39	0.39
24	OCH_3	OCH_3			OCH_3	CH_3	1.73[p]	1.11	0.78	0.33
25	OCH_3		OC_2H_5	OCH_3		CH_3	2.24[q]	1.18	1.37	0.19
26	OCH_3		C_5H_{11}	OCH_3		CH_3	4.31[r]	1.00	1.09	0.09
27		OCH_3	OCH_3			CH_3	1.00[b]	<0.00	−0.52[s]	0.52
28	OCH_3	OCH_3	OCH_3			CH_3	1.36[b]	0.30	0.18[s]	0.12

[a] Log P = log $P_{3,4,5\text{-trimethoxyamphetamine}} - \pi_{\text{branched methyl}}$ = 1.48 − 0.30 = 1.18.
[b] Experimental value, this report.
[c] Log P = log $P_{2,5\text{-dimethoxy-4-ethylamphetamine}} + \pi_{\text{methyl}}$ = 2.81 ± 0.50 = 3.31.
[d] Log P = log $P_{2,5\text{-dimethoxy-4-ethylamphetamine}} + 2\pi_{\text{methyl}}$ = 2.81 + 2(0.50) = 3.81.
[e] Log P = log $P_{\text{amphetamine}} + \pi_{\text{methylenedioxy}}$ = 1.73 − 0.05 = 1.68.
[f] Log P = log $P_{3,4\text{-methylenedioxyamphetamine}} + \pi_{3\text{-methoxy}}$ = 1.68 + 0.12 = 1.80.
[g] Log P = log $P_{3,4\text{-methylenedioxyamphetamine}} + \pi_{2\text{-methoxy}}$ = 1.68 + 0.74 = 2.42.
[h] Log P = log $P_{3,4\text{-methylenedioxyamphetamine}} + \pi_{2\text{-methoxy}'}$ = 1.68 + 0.36 = 2.04.
[i] Log P = log $P_{4\text{-methoxyamphetamine}} + \pi_{\text{methylenedioxy}}$ = 1.77 − 0.05 = 1.72.
[j] Log P = log $P_{3,4\text{-methylenedioxyamphetamine}} + \pi_{2\text{-methoxy}'} + \pi_{3\text{-methoxy}}$ = 1.68 + 0.12 = 2.15.
[k] Log P = log $P_{3,4\text{-methylenedioxyamphetamine}} + \pi_{2\text{-methoxy}} + \pi_{3\text{-methoxy}}$ = 1.68 + 0.74 + 0.12 = 2.54.
[l] Log P = log $P_{2,4,5\text{-trimethoxyamphetamine}} - \pi_{\text{branched methyl}}$ = 1.74 − 0.30 = 1.44.
[m] Log P = log $P_{3,4\text{-methylenedioxyamphetamine}} - \pi_{\text{branched methyl}}$ = 1.68 − 0.30 = 1.38.
[n] Log P = log $P_{2,3\text{-dimethoxyamphetamine}} + \pi_{3\text{-methoxy}}$ = 1.49 + 0.12 = 1.61.
[o] Log P = log $P_{2,3,4\text{-trimethoxyamphetamine}} + \pi_{3\text{-methoxy}}$ = 1.36 + 0.12 = 1.48.
[p] Log P = log $P_{2,4,6\text{-trimethoxyamphetamine}} - \pi_{4\text{-methoxy}} + \pi_{3\text{-methoxy}}$ = 1.57 − (−0.04) + 0.12 = 1.73.
[q] Log P = log $P_{2,4,5\text{-trimethoxyamphetamine}} + \pi_{\text{methyl}}$ = 1.74 + 0.50 = 2.24.
[r] Log P = log $P_{2,5\text{-dimethoxy-4-ethylamphetamine}} + 3\pi_{\text{methyl}}$ = 2.81 + 1.50 = 4.31.
[s] A prediction of the activity based on the calculated log P was made, but the compound was not included in the regression analysis.

Note: π constants were determined for crowded and uncrowded 2-methoxys as follows: $\pi_{2\text{-methoxy (uncrowded)}}$ = log $P_{2,4,5\text{-trimethoxyamphetamine}}$ − log $P_{3,4\text{-dimethoxyamphetamine}}$; $\pi_{2\text{-methoxy}'\text{ (crowded)}}$ = log $P_{2,3,4\text{-trimethoxyamphetamine}}$ − log $P_{3,4\text{-dimethoxyamphetamine}}$.

The hallucinogenic data are from the compilation of Shulgin, *et al.*[16] The activity values of the 4-propyl, 4-butyl, and 4-pentyl derivatives of 2,5-dimethoxyphenylisopropylamine were obtained by personal communication from A. T. Shulgin. The potencies are reported in Mescaline Units, M. U., as defined by Shulgin.[16] The data are given in Table I.

Regression equations were generated using a nonweighted, multivariable, linear regression program and the IBM 370/155 computer of the Research Resources Laboratory of the University of Illinois at the Medical Center.

Results and Discussion

Attempts to relate the hallucinogenic potencies in humans of the psychotomimetic amines resulted in eq 1. The

$$\log \text{act.} = -3.17\ (\pm 1.61) + 3.15\ (\pm 1.33) \log P - 0.50\ (\pm 0.25) \log P^2 \quad (1)$$

$$n = 26;\ r = 0.79;\ s = 0.41;$$

$$\log P_0 = 3.14\ (2.89\text{–}3.72)$$

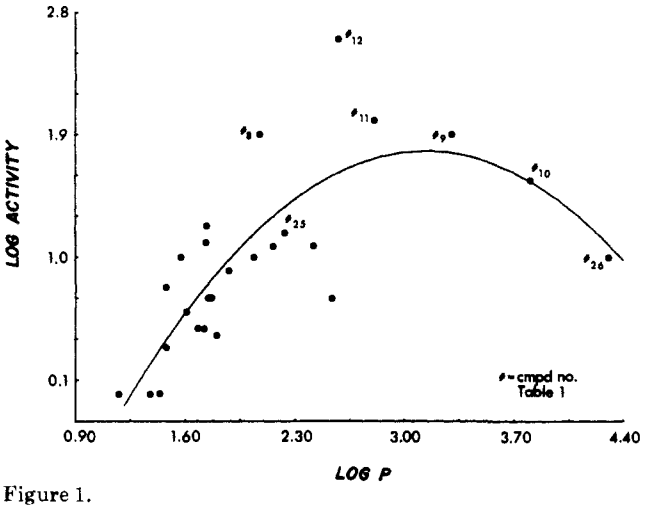


Figure 1.

terms in eq 1 and the statistical parameters are defined as follows: P is the 1-octanol–water partition coefficient, n is the number of agents in the data set, r is the correlation coefficient, and s is the standard deviation of the regression. The optimum lipophilicity, log P_0, is obtained by finding the partial derivative, $\delta(\log \text{act.})/\delta(\log P)$, equating it with zero, and solving for log P. The equation is significant of the 99.5% level of confidence as determined from the F statistic: $F_{2,23} = 19.436$, $F_{2,23:\,\alpha\,0.005} = 6.730$. Figure 1 illustrates eq 1.

The correlation coefficient for our analysis is not as high as one would hope from studies of this nature. Because of variability in the biological data, which is accurate to only ±25%,[16] one can at best expect to account for 75% of the variation. However, our equation accounts for 62% (R^2 = 0.62) of the variation, leaving about 10% for approximations introduced in applying the model and other factors that may effect activity. The best previous correlation using the quantum mechanically derived parameter, HOMO, accounted for 56% of the variance using only 13 of the hallucinogenic drugs. Therefore, our results indicate that lipophilicity is important in determining hallucinogenic potency. Due to the high degree of steric crowding in several of the compounds, there is a degree of uncertainty regarding the applicability of additivity in each case. If anything, however, we believe that inclusion of the calculated log P values gives a regression which tends to be less highly correlated than would be the case for the actual experimentally determined values. For example, regression equations using only the 11 experimental values give approximations for the portion of the curve $0.9 < \log P \leq 2.81$. Both the linear and parabolic regressions have R^2 = 0.83. This value is somewhat better than the overall correlation when the calculated log P values are included.

The optimum lipophilicity is of interest since it predicts that psychotomimetic amines more or less lipophilic than those with log P_0 = 3.14 should have less than optimum activity. To our knowledge an optimum log P has not previously been observed in the analysis of biological data obtained on human subjects. Our finding indicates that this relative affinity for lipoidal biophases is necessary or maximum passive permeation of the CNS. This could be an important physicochemical parameter to consider in the design of active CNS agents.

The studies of Kang and Green[2] indicate that some of the variation in hallucinogenic activity of substituted amphetamines may be due to the electronic nature of the substituents. While our data do not directly support this, the unexplained variance from our analysis does suggest that other factors affect the level of potency. For the substituents in the series electronic effects are difficult to parameterize. For those amphetamines for which potency could be determined with some degree of certainty, a log P of approximately 1.40 is required for activity. The exception to this is mescaline, which indicates that an electronic or other effect may be present. The low to marginal activity of 3,4-dimethoxyamphetamine is interesting since its log P is determined to be 1.00. This is near that of mescaline, which is active. The additional m-methoxy group in mescaline must be responsible for the increased potency. The influence of the methoxy somehow overcomes the effect of lipophilicity even in the absence of a secondary α-methyl group as in the amphetamines.

Amphetamine, with log P estimated to be 1.71, is reported to be inactive as an hallucinogen[2] (except with chronic usage where it precipitates a toxic psychosis), while 2,4,5-trimethoxyamphetamine with log P determined to be 1.74 has significant activity. Since the lipophilicities of these two amphetamines are similar, this would imply that the methoxy substitution contributes in addition to a lipophilic effect, an electronic or chemical effect. However, within the series of hallucinogenic compounds examined, the change in activity due to structural variation appears to result mainly from changes in hydrophobicity. Activity drops off for highly lipophilic methoxy-substituted amphetamines (log $P > 4.00$) as can be noted from the data for the 2,5-dimethoxy-4-pentyl analog. This is consistent with the proposal of Hansch[17] regarding the role of lipophilicity and drug action.

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