(0.35 mm) [lit.[9] 73°,(2.0 mm), 37% yield by Na reduction].

Trans Esters. The trans esters in Table I were all prepd in the usual manner by addn of the acid chloride in PhH to the alcohol and Et_3N in PhH. Nmr ($CDCl_3$) spectra of all trans esters were similar to that of the alcohol. Under triple irradiation, decoupling both CH_2 groups, the vinyl protons of the morpholino pivalate appeared as a singlet (half-bandwidth 3 Hz).

4-Amino-2-butyn-1-ol Esters. The esters in Table II were prepd as above for the trans esters from the corresponding alcohol and acid chloride.

Cis Esters. The cis esters in Table I were prepd by redn with H_2 and 5% Pd/C in EtOH at room temp and atm pressure to the theoretical amt. Usual work-up and distn; nmr ($CDCl_3$) δ 6.04 (octet, 2, half-bandwidth ~28 Hz). Triple irradiation, as above, showed a quartet (J_{AB} = 11.5 Hz).

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Directional Nature of Hydrophobic Bonding in Phenethanolamine *N*-Methyl Transferase Inhibitors†

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When a substrate or an inhibitor is bound by an enzyme it is possible that only part of the small molecule makes contact with the macromolecule. Those parts of the small molecule which do not make contact do not contribute to hydrophobic bonding. While relatively few such examples have been established in quantitative terms for sets of congeners, the example of the emulsin hydrolysis of phenyl glucosides is clear-cut.[1] The recent study of Fuller, *et al.*,[2] provides another example. Table I contains their biological data and substituent constants for a series of ring-substituted amphetamines causing 50% inhibition of phenethanolamine *N*-methyl transferase (PNMT) using norepinephrine as the substrate. Fuller, *et al.*, showed[2] that by omitting 5 derivatives (3-Br, 4-OH; 3-Cl, 4-OH; 3,4-$(OH)_2$; 4-OH; 3-OH) the rest of the data could be correlated in 2 equations each containing a linear term in π and σ. For the equation correlating the 17 3,4 derivatives they obtained a correlation coefficient of 0.843 and for the equation correlating the 12 2 derivatives, r was 0.894. The unsubstituted compound was included in each set.

In reexamining this study in the light of our experience with the emulsin work,[1] it was decided to consider the simple monosubstituted meta and para isomers separately. This yielded eq 1 and 2. In the case of eq 1, dropping the σ term yields an equation with the single variable π having r = 0.734. While adding the term in σ is not justified by an F test (we feel this is due to the small number of data points), the coefficient is reasonably close to that of eq 2. Adding a term in π to eq 2 does not give a significant improvement in correlation and the coefficient with the π term in the two-variable equation is quite small (0.22). Hence we assume no hydrophobic interaction from the 4 position and assign π = 0 for all 4 substituents. Further preliminary work suggested that substituents in the 5 and 6 positions were also not involved in hydrophobic binding. Only 3 derivatives are in this category. For these positions π was also taken to be zero.

meta isomers

	n	r	s	
$pI_{50} = 1.54\pi + 1.98\sigma + 2.51$	5	0.863	0.591	(1)

para isomers

	n	r	s	
$pI_{50} = 1.39\sigma + 3.18$	8	0.861	0.256	(2)

Our model, then, for the fit of the inhibitors into a hydrophobic cleft is that only one side is accommodated. The 4, 5, and 6 positions of the inhibitor stand clear of hydrophobic regions of the enzyme. As far as the 5 and 6 positions are concerned, this is a very tentative conclusion since it is based on only 3 molecules having relatively small variance in π. In order to fit the 2-substituted inhibitors into the same equation we have included a steric term for these substituents (E_{s-2}). In addition to these extrathermodynamic postulates it was found that the 3-MeO function behaves in an anomalous manner. To account for this a dummy parameter of 1.00 was assigned to all 3-MeO functions; other molecules were assigned a value of zero for this parameter. Under these conditions we are able to include all but one of the molecules (3,4-$(OH)_2$) of Table I in the single equation

	n	r	s	
$pI_{50} = 0.485(\pm0.23)E_{s-2} + 0.991(\pm0.36)\pi_{-2,3} + 1.408(\pm0.37)\Sigma\sigma - 1.009 \times (\pm0.33)D + 2.550(\pm0.28)$	32	0.940	0.288	(3)

Equation 3 not only includes all of the data in a single equation instead of 2 equations, but it also has the advantage that we have only had to omit one data point instead of the 5 omitted by the Lilly group. In addition, the correlation with eq 3 is much better (r of 0.940 *vs.* r of 0.843 and 0.894) than either of the 2 equations used in the previous effort to correlate these data.

The directional nature of hydrophobic bonding stands out clearly for the 4 position. For example, the 4-CF_3 and 4-OC_6H_5 are well fit by eq 3 assigning π = 0 to these very lipophilic functions.

In designing more potent inhibitors, one would want to place strong electron-withdrawing groups in the 4 position regardless of their lipophilic nature. In fact, nonlipophilic functions such as NO_2 and CN might be best. The largest possible lipophilic function (with due consideration of

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Table I. Inhibition of PNMT by Ring-Substituted Amphetamines

Substituent	$E_{S\text{-}2}$[a]	$\Sigma\pi_{-2,3}$[b]	$\Sigma\sigma$	D	pI_{50} Obsd[c]	pI_{50} Calcd[d]	$\lvert\Delta pI_{50}\rvert$
3,4-Cl_2	1.24	0.71	0.60	0.00	5.10	4.70	0.40
3-Cl	1.24	0.71	0.37	0.00	4.23	4.38	0.15
4-CF_3	1.24	0.00	0.54	0.00	4.00	3.91	0.09
3,4-F_2	1.24	0.14	0.40	0.00	3.85	3.85	0.00
3-F	1.24	0.14	0.34	0.00	3.75	3.77	0.02
4-Cl	1.24	0.00	0.23	0.00	3.60	3.48	0.12
4-*i*-Pr	1.24	0.00	−0.15	0.00	3.30	2.94	0.36
3-Me	1.24	0.50	−0.07	0.00	3.17	3.55	0.38
4-Me	1.24	0.00	−0.17	0.00	3.14	2.91	0.23
4-F	1.24	0.00	0.06	0.00	3.01	3.24	0.23
H	1.24	0.00	0.00	0.00	2.89	3.15	0.26
3,4-Me_2	1.24	0.50	−0.24	0.00	2.85	3.31	0.46
4-OC_6H_5	1.24	0.00	−0.32	0.00	2.76	2.70	0.06
4-OMe	1.24	0.00	−0.27	0.00	2.57	2.77	0.20
3-OMe	1.24	−0.02	0.12	1.00	2.07	2.29	0.22
3-OMe, 4-OEt	1.24	−0.02	−0.12	1.00	2.06	1.95	0.11
3,4-$(OMe)_2$	1.24	−0.02	−0.15	1.00	2.00	1.91	0.09
3-Br, 4-OH	1.24	0.86	0.02	0.00	4.15	4.03	0.12
3-Cl, 4-OH	1.24	0.71	0.00	0.00	4.15	3.86	0.29
3,4-$(OH)_2$[e]	1.24	−0.67	−0.25	0.00	3.30	2.14	1.16
4-OH	1.24	0.00	−0.37	0.00	3.12	2.63	0.49
3-OH	1.24	−0.67	0.12	0.00	2.77	2.66	0.11
2,4-Cl_2	0.27	0.71	0.45	0.00	4.02	4.02	0.00
2,5-F_2	0.78	0.14	0.40	0.00	3.48	3.63	0.15
2,6-Cl_2	−0.70	0.71	0.45	0.00	3.47	3.55	0.08
2-Me	0.00	0.50	−0.17	0.00	3.25	2.81	0.44
2-Cl	0.27	0.71	0.23	0.00	3.24	3.71	0.47
2-F	0.78	0.14	0.06	0.00	3.17	3.15	0.02
2,4-F_2	0.78	0.14	0.12	0.00	3.08	3.24	0.16
2,4-Me_2	0.00	0.50	−0.34	0.00	2.85	2.57	0.28
2,5-Me_2	0.00	0.50	−0.24	0.00	2.83	2.71	0.12
2,3-$(OMe)_2$	0.69	−0.04	−0.15	1.00	1.65	1.62	0.03
2,4-$(OMe)_2$	0.69	−0.02	−0.54	0.00	1.51	2.11	0.60

[a] See reference 3. [b] π values are from the benzene system; see reference 4. [c] From reference 2. [d] Calcd using eq 3. [e] This point not used in deriving eq 3.

Baker's bulk tolerance principle[5]) should then be placed in the 3 position. For example, if bulk tolerance would allow the use of a 3-Bu function, the 4-NO_2-3-Bu derivative would be more potent than any of the inhibitors of Table I. The predicted pI_{50} is 6.1. If a group as large as hexyl could be accommodated in the 3 position, pI_{50} would be 7.1.

For *in vivo* work $\log P_O$ would set a lower limit on total lipophilic character. Under these conditions the 4-SO_2CH_3 function could be used to balance a 3-Bu or 3-Hex function.

The coefficient with the $\pi_{-2,3}$ term is not uncommon for enzymic hydrophobic bonding.[6,7] The rather large coefficient with the σ term indicates that activity is highly dependent on electron withdrawal by substituents. This might well indicate that an electron-deficient inhibitor benzene ring is interacting with an electron-rich site in the enzyme. The high negative coefficient with D indicates an inexplicable deleterious effect of a 3-MeO function.

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N^1,N^1-Dialkyl-N^4,N^4-dialkylaminoacetylsulfanilamide as Potent Surface Anesthetics

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In a previous communication,[1] we reported the synthesis and potent local anesthetic activity of sulfamoylbenzoic acid ester derivatives of low toxicity. In the present work, we report the synthesis and surface anesthetic activity of a new series of compounds: N^1,N^1-dialkyl-N^4,N^4-dialkylaminoacetylsulfanilamide.

Scheme I