mp 38–40 °C. Anal. ($C_{15}H_{23}N_3S$) C, H, N.

Acknowledgment. The authors thank Dr. K. Senga, Dr. D. E. O'Brien, and Mr. R. H. Springer for helpful suggestions. We also thank Ms. P. F. Dougherty and Mr. D. W. Yotter for determining antimicrobrial data and Mrs. M. Alta and Mr. E. Banta for providing spectra and analytical data.

References and Notes

(1) Presented at the 168th National Meeting of the American Chemical Society, Atlantic City, N.J., 1974, Abstract MEDI 42.
(2) G. R. Revankar, T. R. Matthews, and R. K. Robins, *J. Med. Chem.*, **18**, 1253 (1975).
(3) T. Novinson, J. P. Miller, M. Scholten, R. K. Robins, L. N. Simon, D. E. O'Brien, and R. B. Meyer, Jr., *J. Med. Chem.*, **18**, 460 (1975).
(4) R. H. Springer, M. K. Dimmitt, T. Novinson, D. E. O'Brien, R. K. Robins, L. N. Simon, and J. P. Miller, *J. Med. Chem.*, **19**, 291 (1976).
(5) P. M. Scholz, W. B. Jolley, T. Novinson, J. E. Kaiser, and L. L. Smith, *Surg. Forum*, **23**, 1 (1972).
(6) K. Senga, T. Novinson, R. H. Springer, R. P. Rao, D. E. O'Brien, R. K. Robins, and H. R. Wilson, *J. Med. Chem.*, **18**, 312 (1975).
(7) T. Novinson, B. Bhooshan, T. Okabe, G. R. Revankar, R. K. Robins, K. Senga, and H. R. Wilson, *J. Med. Chem.*, **19**, 512 (1976).
(8) The "7-hydroxypyrazolo[1,5-*a*]pyrimidine" nomenclature is preferred over the "pyrazolo[1,5-*a*]pyridin-7-one" for the reasons described in ref 7 (footnote).
(9) (a) Y. Makisumi, *Chem. Pharm. Bull.*, **10**, 612 (1962); (b) *ibid.*, **12**, 204 (1964).
(10) P. Schmidt and J. Druey, *Helv. Chim. Acta*, 986 (1956).
(11) H. Reimlinger and A. Meryeni, *Chem. Ber.*, **103**, 3252 (1970).
(12) R. S. Gordee and T. R. Matthews, *Antimicrob. Agents Chemother.*, **1967**, 378 (1968).
(13) J. F. Bagli and D. Kluepfel, *J. Org. Chem.*, **38**, 1253 (1973).
(14) H. Gershon, M. W. McNeil, R. Parmegiani, P. K. Godfrey, and J. M. Baricko, *Antimicrob. Agents Chemother.*, **4**, 435 (1973).
(15) V. N. Sokolova, G. A. Modnikova, O. Yu. Mazidson, L. I. Shcherbakova, G. N. Perschin, and T. N. Zykova, *Khim. Pharm. Zh.*, **24**, 19 (1973).
(16) (a) T. Noguchi and H. Okeda, *J. Pharm. Soc. Jpn.*, **76**, 383 (1956); (b) *ibid.*, **76**, 390 (1956).
(17) O. Wyss, B. J. Ludwig, and R. R. Joiner, *Arch. Biochem.*, **7**, 415 (1945).
(18) G. E. W. Wolstenholme and R. Porter, Ed., "Systemic Mycoses", J. A. Churchill Publishing Co., London, 1968, p 206.
(19) H. Dorn and A. Zubek, *Chem. Ber.*, **101**, 3265 (1968).

Lipophilicity and Serotonin Agonist Activity in a Series of 4-Substituted Mescaline Analogues

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Replacement of the 4-methoxy of mescaline with higher alkyl homologues or with bromine led to increased activity at serotonin receptors in a sheep umbilical artery preparation. This activity appears correlated with lipophilicity, as measured by 1-octanol–water partition coefficients, but drops off when the 4-substituent is about five atoms in length. It is suggested that 3,4,5-trisubstitution may give compounds which are as active as those with the 2,4,-5-substitution pattern.

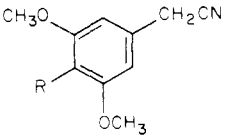
Barfknecht et al.[1] recently reported that a correlation exists between 1-octanol–water partition coefficients and human activity for a series of psychotomimetic phenylisopropylamines. Optimum lipophilicity was reported to be at log $P = 3.14$, a value close to the log P of 2.96 for LSD (W. J. Dunn, III, personal communication). In that study, however, the value of log P estimated for mescaline appeared to place it outside of the range where activity would be expected, and it was suggested that some other parameter was able to compensate for the low lipophilicity.

In an early study of a series of phenethylamines it was shown that in animals the loss of the 5-methoxy from mescaline resulted in reduced activity, while loss of the 4-methoxy abolished activity completely.[2] In humans 3,4-dimethoxyphenethylamine is nonhallucinogenic.[3] Substitution of the 4-methoxy with a benzyloxy[2] or an ethoxy[4] was reported to increase activity. Replacement of the 4-methoxy with a methyl also gives a compound which retains activity.[5] In view of these reports it was decided to examine the possibility that such modifications of the 4-substituent might lead to increased potency as a result of changes in lipophilicity. Although the nature of the 4-substituent has been shown to be important for maximum activity, compounds with a relatively long lipophilic chain at this position show high activity in humans.[6]

This report describes a series of compounds, **3a–f** (Table II), for which 1-octanol–water partition behavior was examined and was related to activity at serotonin receptors in the sheep umbilical artery preparation.[7] This model previously has been shown to have a promising correlation with hallucinogenic activity in man.[7,8]

Chemistry. The phenylacetonitriles, **2a–f**, served as useful intermediates in the synthetic scheme. With the exception of compound **2f**, all were prepared by alkylation of 3,5-dimethoxy-4-hydroxyphenylacetonitrile, obtained in an overall yield of 59% from 2,6-dimethoxyphenol using the method of Short et al.[12] The yields of most alkylations were excellent to good (see Table I), in spite of anticipated steric problems. Reduction of compounds **2a–d** was accomplished catalytically with hydrogen, and compounds **3e,f** were obtained by borohydride–cobalt reduction according to the method of Satoh et al.[13] This latter method appeared to give small amounts of O-debenzylation but

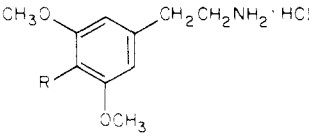
Table I. 3,5-Dimethoxy-4-substituted Phenylacetonitriles



Compd no.	R	Mp or bp (mm), °C	Yield, %	Formula	Analyses
2a	OC_2H_5	57-58	86	$C_{12}H_{15}NO_3$	C, H, N
2b	O-*n*-C_3H_7	112-114 (0.1)	75	$C_{13}H_{17}NO_3$	C, H, N
2c	O-*i*-C_3H_7	33-34	65	$C_{13}H_{17}NO_3$	C, H, N
2d	O-*n*-C_4H_9	42-43	87	$C_{14}H_{19}NO_3$	C, H, N
2e	$OCH_2C_6H_5$	66-67[a]	84	$C_{17}H_{17}NO_3$	
2f	Br	125-126	84[b]	$C_{10}H_{10}BrNO_3$	C, H, N

[a] Lit.[18] mp 64-65 °C. [b] Based on the chloride 6.

Table II. 3,5-Dimethoxy-4-substituted Phenethylamine Hydrochlorides



Compd no.	R	Mp, °C	Yield, %	Formula	Analyses
3a	OC_2H_5	166-167[a]	82	$C_{12}H_{20}ClNO_3$	
3b	O-*n*-C_3H_7	170-172	80	$C_{13}H_{22}ClNO_3$	C, H, N
3c	O-*i*-C_3H_7	163-164	69	$C_{13}H_{22}ClNO_3$	C, H, N
3d	O-*n*-C_4H_9	155-157[b]	76	$C_{14}H_{24}ClNO_3$	C, H, N
3e	$OCH_2C_6H_5$	162-163[c]	66	$C_{17}H_{22}ClNO_3$	
3f	Br	241 dec	49	$C_{10}H_{15}BrClNO_3$	C, H, N

[a] Lit.[19] mp 165-166 °C. [b] See ref 20. [c] Lit.[18] mp 156-158 °C.

Table III. Potency Ratios and Log *P* Values for 3,5-Dimethoxy-4-substituted Phenethylamine Hydrochlorides

Compd no.	*n*	ED_{50}, M	Potency ratio	Log *P*	Log potency
Mescaline	7	1.4×10^{-6} (1.0-1.8)	1.00	0.78	0.00
3a	6	6.8×10^{-7} (6.0-7.5)	2.06	1.11	0.31
3b	6	3.8×10^{-7} (2.8-5.1)	3.68	1.70	0.56
3c	5	5.0×10^{-7} (4.0-6.0)	2.80	1.52	0.45
3d	6	1.1×10^{-6} (0.81-1.3)	1.27	2.32	0.10
3e	6	4.6×10^{-7} (3.6-6.0)	3.04	2.40	0.48
3f	6	1.85×10^{-7} (1.35-2.5)	7.57	2.03	0.88

apparently did not result in aromatic debromination in the reduction of **2f**, as might be expected using lithium aluminum hydride[14] or catalytic reductive procedures. The synthesis of compound **2f** was accomplished in four steps proceeding from commercially available 3,5-dihydroxy-4-bromobenzoic acid. Physical data for the amine salts are given in Table II.

Results and Discussion

As shown in Table III, all compounds were more potent than mescaline in this preparation. There is a regular increase in activity which seems related to increasing log *P* up to compounds **3d** and **3e**. Activity then drops off markedly. The log *P* values of 2.32 and 2.40, respectively, are below the expected value for optimum activity,[6] and we believe this indicates that the receptor is unable to accommodate a para substituent which is longer than about four atoms. This would be in agreement with the data of Morin et al.[15] who found that in a homologous series of 2,5-dimethoxy-4-*n*-alkylphenylisopropylamines activity was completely lost in going from the *n*-butyl to the *n*-pentyl homologue. Both *n*-butoxy and benzyloxy are similar in length to an *n*-pentyl.

It is well established that congeneric series of drugs have an optimum degree of lipophilic character and that large deviations from this optimum lead to reduced activity.[16] Based on earlier studies we would predict compounds with optimum activity at log *P* values near 3.[6] None of the compounds in this series had a value that high but they were of an order to expect reasonable activity. Although attempts to develop regression equations gave promising results, the number of data points was judged insufficient to draw meaningful conclusions.

It is interesting to speculate regarding the ability of serotonin receptors in this preparation to accept lipophilic groups in the para position of phenethylamine derivatives. It is possible that such moieties may be accommodated on the receptor by the relatively larger binding site for the indole nucleus of serotonin. However, as suggested by this work, there appear to be steric limits to this binding ability.

In conclusion, this study has shown that appropriate manipulation of lipophilic character can lead to increased activity in 3,4,5-trisubstituted compounds. It should be pointed out that the log *P* of mescaline is even lower than was originally estimated.[1] It is suggested that this substitution pattern leads to compounds which are intrinsically at least as active as compounds with 2,4,5-trisubstitution. The report[3] that 2,4,5-trisubstitution gives compounds of highest activity may simply reflect the fact that 3,4,5-substituted compounds of comparable log *P* had not been examined.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. IR spectra were obtained with a Beckman IR-33, and NMR spectra were recorded on a Varian EM-360 instrument.

Elemental analyses were performed by PCR, Inc., Gainsville, Fla., or the microanalysis laboratory, Chemistry Department, Purdue University, and were within ±0.4% of the calculated values.

Partition Coefficients. Partition coefficients were determined in 1-octanol–water as described previously,[9] using 0.1 M pH 8 phosphate buffer as the aqueous phase. Partition coefficients are reported for the neutral species, with correction for ionization by the method of Albert.[10] The reported pK_a for mescaline of 9.56[11] was used for correction of all compounds. Regression equations were generated using a nonweighted, polynomial regression program and a Hewlett-Packard 9810 programmable calculator.

Effects on Sheep Umbilical Artery Strips. All comparisons were made on isolated sheep umbilical arteries as described previously.[7] Artery strips were initially contracted maximally by adding mescaline in a cumulative manner. The tissues were then repeatedly washed until they relaxed. The test compound was then added to each tissue bath in a cumulative manner. The ED_{50} values were obtained from dose–response curves and are the concentrations of agonists required to produce 50% of the maximum mescaline-induced contraction. The ratio (ED_{50} mescaline/ED_{50} compound) given is based on actual data for each series of experiments. These data are given in Table III where n is the number of tissues, and numbers in brackets indicate the standard error of the geometric mean.

A time control using mescaline indicated that the dose–response curve shifted to the right about 3.4-fold. Thus, the actual potency values may be higher than indicated.

3,5-Dimethoxy-4-hydroxyphenylacetonitrile (1). This material was obtained in overall yield of 59% by the method of Short et al.[12] and had bp 156–158 °C (0.05 mm) [lit.[12] bp 144–145 °C (0.33 mm)] and mp 57–58 °C (no literature melting point reported). The material could also be purified by recrystallization of the 1:1 $CHCl_3$ solvate from $CHCl_3$–hexane.

3,5-Dimethoxy-4-alkoxyphenylacetonitriles. General Procedure. 2a–e. The nitrile 1 (0.03 M), 0.08 M of the appropriate alkyl iodide (or benzyl bromide), and 0.05 M of anhydrous K_2CO_3 were stirred together under reflux in 50 ml of dry acetone for 18 h. The mixture was diluted with 2 vol of ether and filtered, and the filtrate reduced under vacuum. The residue was either recrystallized from ether–hexane or vacuum distilled. Yields reported in Table I are final yields of pure product.

3,5-Dimethoxy-4-bromobenzyl Alcohol (5). Methyl 3,5-dimethoxy-4-bromobenzoate[17] was reduced with $LiAlH_4$ in ether in the usual way. After work-up the desired benzyl alcohol was recrystallized from ether to give a 91% yield of material with mp 103–104 °C. Anal. ($C_9H_{11}BrO_3$) C, H.

3,5-Dimethoxy-4-bromobenzyl Chloride (6). The alcohol **5**, 12.35 g (0.05 M), was added all at once to 200 ml of concentrated HCl. The mixture was vigorously stirred at room temperature for 7 h. The reaction was then suction filtered and the solid collected on sintered glass. The filtrate was extracted with 2 × 50 ml of C_6H_6. The solid was dissolved in C_6H_6 and the organic solutions were combined, placed in a separatory funnel, and as much of the aqueous acid layer separated as possible. The resulting C_6H_6 solution was dried ($MgSO_4$), filtered, and reduced under vacuum. On cooling the residue solidified and was triturated with cold petroleum ether and filtered to yield 11.71 g (88%) of material which showed only trace starting material on TLC analysis. An analytical sample was recrystallized from hexane: mp 69 °C. Anal. ($C_9H_{10}BrClO_2$) C, H.

3,5-Dimethoxy-4-bromophenylacetonitrile (2f). The chloride **6**, 5.3 g (20 mM), was added, portionwise, to a stirring suspension of 1.1 g (22.5 mM) of NaCN in 8 ml of Me_2SO. The mixture was held at 50 °C for 0.5 h and was then stirred at room temperature for 4 h. TLC (silica gel–$CHCl_3$) showed essentially quantitative conversion to the nitrile. The mixture was diluted to 75 ml with H_2O and filtered. The resulting yellow solid was taken up into the minimum amount of Et_2O (ca. 250 ml) and the ether solution washed with 3 × 50 ml of saturated NaCl solution, dried ($MgSO_4$), and reduced under vacuum. The residue was recrystallized from ether to yield 4.3 g (84%) of nitrile: mp 125–126 °C. Anal. ($C_{10}H_{10}BrNO_2$) C, H, N.

Preparation of Amines. Method A.[12] The nitrile (**2a–d**) (0.01 M) was dissolved in 25 ml of EtOH + 2.5 ml of concentrated HCl and shaken at 50 psi of H_2 over 400 mg of 10% Pd/C. The mixture was shaken for 24 h and filtered (Celite), the solvents were removed under vacuum, and the residue was recrystallized from i-PrOH–Et_2O. Recrystallized yields are given in Table II.

Preparation of Amines. Method B[13] **(2e,f).** The nitrile (0.01 M) and 4.76 g of $CoCl_2 \cdot 6H_2O$ were dissolved in 60 ml of MeOH. Sodium borohydride (3.8 g) was added over 15 min, with cooling to keep the temperature at 30–40 °C. Stirring was continued for 1 h at room temperature. To the mixture was then added 20 ml of concentrated HCl and the reaction reduced in vacuo. The residue was dissolved in 75 ml of H_2O and extracted with 2 × 30 ml of Et_2O. A small amount of insoluble material was removed by filtration. The H_2O layer was then made basic with excess concentrated NH_4OH and extracted with 3 × 25 ml of $CHCl_3$. The $CHCl_3$ layers were combined, dried (Na_2SO_4), and reduced under vacuum. The residual oil was taken up into dry ether and precipitated by addition of 5% HCl–EtOH. The hydrochloride salt was recrystallized from EtOH–Et_2O. Yields are reported in Table II.

Acknowledgment. This work was supported in part by general research support funds from the School of Pharmacy and Pharmacal Sciences, Purdue University (D.E.N.), and by grants from the Washington State Heart Association and the Iowa Heart Association (D.C.D.). The authors thank Dr. W. Wagner for his cooperation in supplying the sheep tissues used in this study. The authors also acknowledge many helpful discussions with Dr. W. J. Dunn, III.

References and Notes

(1) C. F. Barfknecht, D. E. Nichols, and W. J. Dunn III, *J. Med. Chem.*, **18**, 208 (1975).
(2) J. R. Smythies and C. K. Levy, *J. Ment. Sci.*, **106**, 531 (1960).
(3) A. T. Shulgin, T. Sargent, and C. Naranjo, *Nature (London)*, **221**, 537 (1969).
(4) G. S. Grace, *J. Pharmacol. Exp. Ther.*, **50**, 359 (1934).
(5) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **25**, 2066 (1960).
(6) A. T. Shulgin and D. C. Dyer, *J. Med. Chem.*, **18**, 1201 (1975).
(7) D. C. Dyer, D. E. Nichols, D. B. Rusterholz, and C. F. Barfknecht, *Life Sci.*, **10**, 885 (1973).
(8) D. C. Dyer and D. W. Gant, *J. Pharmacol. Exp. Ther.*, **184**, 366 (1973); D. C. Dyer, *ibid.*, **188**, 336 (1974).
(9) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).
(10) A. Albert, "Selective Toxicity", 2d ed, Wiley, New York, N.Y., 1960.
(11) R. J. Taska and J. C. Schoolar, *Arch. Int. Pharmacodyn. Ther.*, **202**, 66 (1973).
(12) J. H. Short, D. A. Dunnigan, and C. W. Ours, *Tetrahedron*, **29**, 1931 (1973).
(13) T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, and Z. Imai, *Tetrahedron Lett.*, 4555 (1969).
(14) C. F. Barfknecht and D. E. Nichols, *J. Med. Chem.*, **14**, 370 (1971).
(15) R. D. Morin, F. Benington, S. R. Mitchell, J. M. Beaton, R. J. Bradley, and J. R. Smythies, *Experientia*, **31**, 93 (1975).
(16) C. Hansch and J. M. Clayton, *J. Pharm. Sci.*, **62**, 1 (1973).
(17) H. Erdtman and B. Leopold, *Acta. Chem. Scand.*, **2**, 34 (1948).
(18) A. Brossi, M. Baumann, and R. Borer, *Monatsh. Chem.*, **96**, 25 (1965).
(19) F. Benington, R. D. Morin, and L. C. Clarke Jr., *J. Am. Chem. Soc.*, **76**, 5555 (1954).
(20) British Patent 360 266 (Jan 8, 1930) [*Chem. Abstr.*, **27**, 513 (1933)] makes reference to this compound, but no physical or biological data are reported.