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A Quantitative Structure–Activity Study of Anticonvulsant Phenylacetanilides

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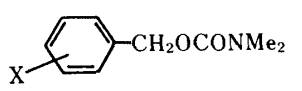
A series of *o*-, *m*-, and *p*-substituted anilides of phenylacetic acid were tested for anticonvulsant activity in mice by means of the maximal electroshock seizure test and structure–activity relationships were quantitatively studied by Hansch analysis. The potencies ($-\log ED_{50}$) for *meta* derivatives were shown to depend parabolically on $\log P$ (P is the 1-octanol–H_2O partition coefficient) and linearly on the Hammett σ values. The derived correlation predicted that the maximum activity would be obtained when $\log P$ is about 2.3 and an electron-donating substituent is introduced. This conclusion is consistent with the structural requirements recently reported for *m*- and *p*-substituted benzyl *N*, *N*-dimethylcarbamates. Most of the *o*- and *p*-substituted compounds exhibited lower activities than *m*-derivatives. The effects of *ortho* and *para* substitutions are discussed.

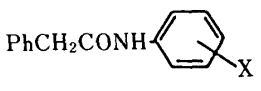
Keywords——structure–activity relationship; Hansch analysis; anticonvulsant activity; substituted phenylacetanilide; optimum hydrophobicity; proximity effect; Hammett's σ value

We previously reported a quantitative structure–activity relationship (QSAR) for anticonvulsant benzyl *N*, *N*-dimethylcarbamates (I).[1] The derived Hansch-type correlation indicated that the maximum potency would be obtained when a compound has a hydrophobicity ($\log P$) of around 1.8 and also has an electron-donating and/or non-hydrogen bonding substituent X on the benzene ring. It was also suggested that the amide group is important for the activity.

With these considerations in mind, we tested the activity of various structurally related amides and found that phenylacetanilide (II, X=H) has a greater potency. It is of interest to examine whether or not the structure–activity relationship for this series of compounds is similar to that for (I). In particular, it is important to know how the potency of the congeners depends on $\log P$, because the hydrophobic property is often a dominant parameter in QSAR of central nervous system (CNS) drugs, as found in the case of benzylcarbamates (I).



I



II

Chart 1

As a preliminary, we recently prepared *m*- and *p*-substituted anilides of phenylacetic acid (II) and carried out systematic studies of the electronic[2] and hydrophobic[3] properties of the compounds with various substituents. In this work, *o*-, *m*-, and *p*-derivatives of (II) were tested

for anticonvulsant activities by the maximal electroshock seizure (MES) method in mice, and the substituent effects on the activities were analyzed by means of Hansch analysis.[4]

A comparison of the results with those obtained for benzylcarbamates (I) allowed us to deduce some structural requirements of anticonvulsant amides for the appearance of the activity and for maximum potency.

Materials and Methods

Materials——All the compounds examined in this study are summarized in Table I. The preparation of most of the *m*- and *p*-derivatives of (II) was previously described.[2] The others were prepared similarly unless otherwise noted. Compounds **17** and **19** were obtained by the esterification of **9** with acetyl chloride and methanesulfonyl chloride, respectively. To obtain the monoalkyl amino derivatives, **11** and **12**, the amino group of **10** was protected with a trifluoromethyl group, then alkylation was carried out according to the procedure described by Johnstone.[5] The structures were identified by nuclear magnetic resonance (NMR, Varian XL-200 spectrometer), infrared (IR) (Hitachi 295 IR spectrometer), and mass (MS) (Hitachi M-80 MS spectrometer) spectroscopic studies and by elemental analyses.

Anticonvulsant Activity——The ED_{50} values (mol/kg) evaluated by the MES test in male ddY strain mice were used as the index of anticonvulsant activity. The method is similar to that described previously,[1] except for the use of carboxymethyl cellulose sodium salt (CMC-Na) solution as the vehicle instead of sesame oil because the compounds are insoluble in the latter. The test compounds were suspended in 1% CMC-Na solution containing 0.85% NaCl and injected intraperitoneally 15 min prior to electroshock.

Partition Coefficient——The log *P* values of *m*- and *p*-derivatives were taken from our previous work.[3] Those of *o*-derivatives were newly determined by the same method.[3,6]

Correlation Analysis——Relationships between anticonvulsant activity and physicochemical parameters were analyzed by fitting the parameters to eq. 1,

$$-\log ED_{50} = -k(\log P)^2 + k'(\log P) + \rho\sigma + \sum e_i E_i + \text{const.} \quad (1)$$

where *P* is the octanol–water partition coefficient, σ is the Hammett electronic constant and E_i represents parameters for other effects such as steric and proximity effects. The σ values were used throughout this study because they gave

TABLE I. Anticonvulsant Activity of Substituted Phenylacetanilides (II)

No.	X	mp[a] (°C)	ED_{50} (95% confidence limits) μmol/kg	No.	X	mp[a] (°C)	ED_{50} (95% confidence limits) μmol/kg
1	H	118	170 (143—203)	**21**	*p*-F	139—140	325 (254—416)
2	*m*-Me	80—81	176 (121—257)	**22**	*p*-OH[b]	172—173	192 (151—244)
3	*m*-Et[b]	73	215 (163—284)	**23**	*p*-OMe	123	165 (103—265)
4	*m*-F	97	460 (297—712)	**24**	*p*-COMe[b]	120—122	308 (259—367)
5	*m*-Cl	91—93	395 (318—491)	**25**	*o*-F	101	334 (303—368)
6	*m*-Br	106—107	478 (334—683)	**26**	*o*-OH[b]	156—157	465 (344—628)
7	*m*-I[b]	118	2290 (1490—3520)	**27**	*o*-NH_2[b]	176	400 (248—644)
8	*m*-CF_3	84	1440 (844—2460)	**28**	*o*-OMe[b]	85	375 (278—505)
9	*m*-OH	134—135	265 (202—347)	**29**	*o*-NO_2	83	511 (414—630)
10	*m*-NH_2	139—140	155 (125—193)	**30**	*o*-COMe	77—78	388 (336—448)
11	*m*-NHMe[b]	85	92.3 (81.0—105)	**31**	*o*-Me	162—163	973 (431—2198)
12	*m*-NHEt[b]	82—84	123 (107—141)	**32**	*o*-$CONH_2$	115	94.0 (85.1—104)
13	*m*-OMe	83—84	280 (225—349)	**33**	*p*-Cl	170	>2000
14	*m*-CN[b]	152	361 (324—402)	**34**	*p*-Br	182	>2000
15	*m*-NO_2	138—139	242 (214—274)	**35**	*p*-CN	163—165	>2000
16	*m*-COMe	129—130	112 (99 0—126)	**36**	*p*-NO_2	131	>2000
17	*m*-OAc[b]	102—104	332 (304—362)	**37**	*p*-$OCHMe_2$	108	>2000
18	*m*-OEt	95—96	380 (280—516)	**38**	*p*-Et	116	>2000
19	*m*-OSO_2Me[b]	103—105	170 (129—223)	**39**	*o*-Cl	129	>2000
20	*p*-Me[b]	134	549 (358—841)	**40**	*o*-Br	123	>2000

a) All melting points are uncorrected. *b*) New compounds.

better results than σ^0 and σ^-. The additional parameters used for calculations will be described later. The intercept, k, k' and e_i were determined by the least-squares method.

Results

The compounds and the parameters used in this study are listed in Table II. The results obtained by regression analysis are summarized in Table III. Correlations between the parameters used are insignificant, as shown in Table IV. Most of the *m*-substituted compounds exhibited activity. However, among many *p*-substituted derivatives examined, only a few of them (shown in Table I) were active. We therefore first tried to perform analyses of the *m*-series alone, and obtained eqs. 2—4 in Table III. Among these eq. 4 gave the best correlation for the *m*-series. The correlation derived for the set of *m*- and *p*-derivatives (**1**—**24**) by using the same parameter terms as in eq. 4 is given by eq. 5, being inferior to eq. 4.

Examination of the deviations of the activity data from the correlations shows that eq. 5 overestimates the potency of all *p*-substituted compounds studied. An attempt to introduce an indicator variable I_p, which takes the value of one for *p*-derivatives and zero for others, yielded an improved correlation, eq. 6. The addition of the I_p term is justified at better than 95% level of significance as examined by the F test. It is noteworthy that the coefficients of each term in eq. 6, rather than eq. 5, closely resemble those in eq. 4.

The analyses including *o*-derivatives gave eqs. 7—9. Since proximity effects are presumed to play significant roles in the activity of *o*-derivatives, attempts to separate the *ortho* effects were made in terms of steric and proximity electronic parameters such as E_s, R and F, and their combinations. Among these, the combination of E_s and R was found to be significant for steric and electronic effects, respectively, giving eq. 9, where σ_p was used for *ortho* substituent ($\sigma_0 = \sigma_p$),[7] and the E_s and R terms are applicable only to *ortho* substituents and are otherwise null. The compounds **31** and **32** were omitted from calculations because of their pronounced deviations from all correlations regarded as significant. The reason will be discussed later.

Discussion

We previously formulated eq. 10 for anticonvulsant activity of *m*- and *p*-substituted benzyl *N*, *N*-dimethylcarbamates,

$$-\log \mathrm{ED}_{50} = -0.209(\log P)^2 + 0.761(\log P) - 0.316\sigma^0 - 0.179HB + 2.952 \qquad (10)$$

where HB is the hydrogen bonding indicator variable ($HB = 0$ for non-hydrogen bonders and $HB = 1$ for hydrogen bonders).

The activity of phenyl acetanilides (II) is described by eqs. 4, 6 and 9, where the HB hydrogen bonding parameter is insignificant. The relative potencies are mainly governed by the hydrophobicity of the molecules when steric effects are not important. Parabolic dependence on $\log P$ provides an optimum hydrophobicity, $\log P_0 \simeq 2.3$, which is very close to those ($\log P_0 = 1.7 - 2.0$) reported for anticonvulsant activity of benzylcarbamates (I)[1] and hydantoins,[8] and also for hypnotic activity of barbiturates.[9] It is interest to note that the above-mentioned compounds, having different frameworks, all have an amide group as the common moiety.

As to the electronic effects, fairly small negative ρ values, -0.35——-0.43, were again observed as in the case of carbamates (I), which is consistent with the hypothesis that electron migration from the amide group to an electron-deficient center on the target site is involved in the critical process.[1] A negative ρ value indicates that an electron-donating substituent is favored to increase the activity.

The physical meaning of the indicator variable I_p is not clear at present. Sterically bulkier

TABLE II. Anticonvulsant Activity and Physicochemical Parameters of Substituted Phenylacetanilides (II)

No.	X	$-\log ED_{50}$ [a]	log P	σ [b]	I_p [c]	E_s [b]	R [b]	Eq. 4 Calcd (Diff.) [d]	Eq. 6 Calcd (Diff.) [d]	Eq. 9 Calcd (Diff.) [d]
1	H	3.77	2.70	0.0	0.00			3.80 (−0.03)	3.79 (−0.02)	3.78 (−0.01)
2	*m*-Me	3.75	3.14	−0.07	0.00			3.68 (0.07)	3.64 (0.11)	3.64 (0.11)
3	*m*-Et	3.67	3.47	−0.07	0.00			3.48 (0.19)	3.44 (0.23)	3.44 (0.23)
4	*m*-F	3.34	3.10	0.34	0.00			3.52 (−0.18)	3.52 (−0.18)	3.52 (−0.18)
5	*m*-Cl	3.40	3.61	0.37	0.00			3.19 (0.21)	3.19 (0.21)	3.19 (0.21)
6	*m*-Br	3.32	3.77	0.39	0.00			3.05 (0.27)	3.05 (0.27)	3.05 (0.27)
7	*m*-I	2.64	3.91	0.35	0.00			2.94 (−0.30)	2.93 (−0.29)	2.94 (−0.30)
8	*m*-CF_3	2.84	3.84	0.43	0.00			2.97 (−0.13)	2.97 (−0.13)	2.98 (−0.14)
9	*m*-OH	3.58	2.22	0.12	0.00			3.78 (−0.20)	3.80 (−0.22)	3.80 (−0.22)
10	*m*-NH_2	3.81	1.58	−0.16	0.00			3.73 (0.08)	3.76 (0.05)	3.79 (0.02)
11	*m*-NHMe	4.03	2.31	−0.30	0.00			3.97 (0.06)	3.95 (0.08)	3.95 (0.08)
12	*m*-NHEt	3.91	2.59	−0.24	0.00			3.92 (−0.01)	3.90 (0.01)	3.89 (0.02)
13	*m*-OMe	3.55	2.86	0.12	0.00			3.71 (−0.16)	3.70 (−0.15)	3.69 (−0.14)
14	*m*-CN	3.44	2.75	0.56	0.00			3.55 (−0.11)	3.58 (−0.14)	3.57 (−0.13)
15	*m*-NO_2	3.62	2.93	0.71	0.00			3.43 (0.19)	3.47 (0.15)	3.46 (0.16)
16	*m*-COMe	3.95	2.62	0.38	0.00			3.66 (0.29)	3.67 (0.28)	3.67 (0.28)
17	*m*-OAc	3.48	2.37	0.39	0.00			3.67 (−0.19)	3.70 (−0.22)	3.70 (−0.22)
18	*m*-OEt	3.42	3.23	0.10	0.00			3.56 (−0.14)	3.54 (−0.12)	3.53 (−0.11)
19	*m*-OSO_2Me	3.77	2.32	0.39	0.00			3.67 (0.10)	3.71 (0.06)	3.71 (0.06)
20	*p*-Me	3.26	3.05	−0.17	1.00				3.50 (−0.24)	3.49 (−0.23)
21	*p*-F	3.49	2.86	0.06	1.00				3.50 (−0.01)	3.49 (0.00)
22	*p*-OH	3.72	1.82	−0.37	1.00				3.69 (0.03)	3.71 (0.01)
23	*p*-OMe	3.78	2.49	−0.27	1.00				3.70 (0.08)	3.70 (0.08)
24	*p*-COMe	3.51	2.75	0.50	1.00				3.38 (0.13)	3.37 (0.14)
25	*o*-F	3.48	2.62	0.06	0.00	−0.46	−0.34			3.44 (0.04)
26	*o*-OH	3.33	2.40	−0.37	0.00	−0.55	−0.64			3.42 (−0.09)
27	*o*-NH_2	3.40	1.45	−0.66	0.00	−0.61	−0.68			3.35 (0.05)
28	*o*-OMe	3.43	2.68	−0.27	0.00	−0.55	−0.51			3.41 (0.02)
29	*o*-NO_2	3.29	2.73	0.78	0.00	−1.01	0.16			3.32 (−0.03)

30	*o*-COMe	3.41	2.90	0.50	0.00	−1.01[f]	0.20	3.39	(0.02)
31	*o*-Me[e]	3.01	2.45	−0.17	0.00	−1.24	−0.13	3.53	(−0.52)
32	*o*-$CONH_2$[e]	4.03	1.95	0.36	0.00	−1.01[f]	0.14	3.50	(0.53)

a) ED_{50}, mol/kg. *b*) Taken from C. Hansch and A. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology," Wiley-Interscience, New York, 1979. *c*) See the text. *d*) Diff., the difference between observed and calculated values. *e*) Omitted from the calculation. *f*) Estimated from data for closely related substituents.

TABLE III. Developments of the Correlation Equations for the Anticonvulsant Activity of Phenylacetanilides (II)

$$-\log ED_{50} = -k(\log P)^2 + k'(\log P) + \rho\sigma + iI_p + \delta E_s + \gamma R + \text{Const.}$$

Series	k	k'	ρ	i	δ	γ	Const.	$\log P_0$	n[a]	r[b]	s[c]	$F_{1,x}$[d]	Eq. No.
		−0.401					4.708		19	0.715	0.253	17.809	2
		(0.200)[e]					(0.596)						
	0.280	1.216					2.480		19	0.801	0.224	5.785	3
meta	(0.247)	(1.436)					(2.034)						
	0.308[f]	1.447[h]	−0.426[h]				2.142[g]	2.35	19	0.862	0.196	5.869	4
	(0.219)	(1.280)	(0.375)				(1.815)						
	0.258	1.143	−0.251				2.508		24	0.808	0.204	(11.92)	5
	(0.200)	(1.156)	(0.321)				(1.626)						
meta, para	0.292	1.321[g]	−0.348[h]	−0.223[h]			2.346	2.26	24	0.850	0.187	4.769	6
	(0.187)	(1.077)	(0.310)	(0.214)			(1.505)						
	0.264	1.222	−0.161	−0.079			2.280		30	0.700	0.228	(5.99)	7
	(0.187)	(1.064)	(0.294)	(0.239)			(1.468)						
	0.290	1.309	−0.135	−0.157	0.404		2.311		30	0.800	0.195	10.050	8
ortho, meta, para	(0.161)	(0.916)	(0.253)	(0.212)	(0.263)		(1.261)						
	0.276	1.229	−0.353[g]	−0.223[h]	0.278[h]	0.621[g]	2.478	2.23	30	0.855	0.172	7.826	9
	(0.143)	(0.812)	(0.275)	(0.193)	(0.251)	(0.459)	(1.122)						

a) Number of points used for correlations. *b*) Correlation coefficient. *c*) Standard deviation. *d*) Figures in parentheses are the values of $F_{m,n-m-1}$ (m=the number of parameters), eq. 2: $F_{1,17:\alpha=0.005}=10.4$, eq. 3: $F_{1,16:\alpha=0.05}=4.49$, eq. 4: $F_{1,15:\alpha=0.05}=4.54$, eq. 5: $F_{3,20:\alpha=0.005}=5.82$, eq. 6: $F_{1,19:\alpha=0.05}=4.38$, eq. 7: $F_{4,25:\alpha=0.005}=4.43$, eq. 8: $F_{1,24:\alpha=0.005}=9.55$, eq. 9: $F_{1,23:\alpha=0.025}=5.75$. *e*) Figures in parentheses are 95% confidence intervals. *f*—*h*) The terms of eqs. 4, 6 and 9 are justified above the 99.5% level unless otherwise noted: *f*) justified at the 99.0% level, *g*) justified at the 97.5% level, and *h*) justified at the 95.0% level.

TABLE IV. Simple Correlation Matrix for the Parameters of Eq. 9

	$\log P$	$(\log P)^2$	σ	E_s	R	I_p
$\log P$	1.000					
$(\log P)^2$	0.989	1.000				
σ	0.495	0.458	1.000			
E_s	0.196	0.207	−0.020	1.000		
R	0.352	0.321	0.585	0.329	1.000	
I_p	−0.132	−0.150	−0.215	0.210	0.135	1.000

groups such as Cl, Br, CN, NO_2 and Et in the *para* position lead to inactive compounds, whereas the corresponding *m*-substituted derivatives are all active. One plausible explanation for this distinct difference is that there is a certain limit in the total length of the molecule which can be accommodated at the active site and once this limit is exceeded, activity is lost. This assumption was supported by the results for compounds of shorter length, $C_2H_5CONHC_6H_4X$(X=*p*-Me, *p*-NO_2, *p*-Br and H), all of which show moderate activities ($-\log ED_{50}$ = 3.49, 3.52, 3.48 and 3.36).[10] The similar finding that large *p*-substituents result in loss of the biological activity was reported for phenoxyacetic acid-type plant growth regulators.[11] The use of the steric parameter L (L is defined as the length of the substituent along the axis of the bond between the first atom of the substituent and the parent molecule) instead of the indicator variable I_p, however, did not improve the correlation.

For *ortho*-substituted compounds, the positive coefficient of E_s seems to reflect steric hindrance to the critical interaction between the reaction center (amide group) and the active site on the biophase, resulting in steric retardation. The steric inhibition of resonance by the *ortho* substituent is also thought to be involved, judging from the positive contribution of the R term. When σ_p is used to describe the electronic effects of *ortho* substituents, it may cause underestimation of the inductive component and overestimation of the resonance component when significant steric hindrance of *ortho* substituents is involved.[7] The R term with a positive coefficient, in contrast to a negative ρ value, seems to reduce the resonance component in the $\rho\sigma$ term.

The activities of *ortho*-Cl and *ortho*-Br derivatives were too weak to be measured. This suggests that the introduction of a large and highly hydrophobic group in the *ortho* position is unfavorable in orienting the molecule for interaction with the receptor site. The fact that the *ortho*-Me derivative is far less active than predicted by eq. 9 can be understood on the same basis.

It is worth noting that similar correlations were derived for two different systems, benzylcarbamates (I) and phenylacetanilides (II). General structural requirements for increasing the anticonvulsant activity are that the hydrophobicity ($\log P$) is around 2 and that the amide moiety is activated by electron supply from an electron-donating substituent. We note that the most active compound **11** in this study, being as active as phenobarbital sodium and over ten times as active as sodium dipropylacetate,[12] satisfies these conditions quite closely.

The similarity in structure–activity relationships between the two systems made us wonder whether or not the oxygen atom adjacent to the amide group in carbamates, $\underline{O}CON=$, is necessary for activity. In order to solve this problem, we tested the sulfurcontaining analogue, $PhCH_2SCONMe_2$, and found that it is similar in activity as well as hydrophobicity to the reference benzyl carbamate (I, X=H). Taking into account that the difference in electronic effects between O and S produces little variation in activity, it may be safely concluded that the presence of the oxygen atom plays no important role in the mechanism of action of the carbamates and, therefore, that the behavior of the amides and the

carbamates can be discussed on an equal basis.

Compound **32** exhibits much greater activity than predicted. This is probably because the $CONH_2$ substituent could compete for the reaction center with the CONH moiety in the parent molecule to produce the anticonvulsant activity.

The results obtained in this study should be helpful in designing new types of anticonvulsants or other CNS-depressant amides. The function of the aromatic ring in determining the activity is still obscure, and further work is planned to elucidate this.

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