[Chem. Pharm. Bull. 33(6)2403—2410(1985)]

Quantitative Structure–Activity Relationships of Anticonvulsant Aralkyl and Alkyl Carbamates

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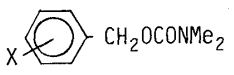
(Received October 1, 1984)

A series of aralkyl and alkyl carbamates of the type $R_1OCONR_2R_3$ (R_1 = alkyl or aralkyl, R_2, R_3 = H, Me, Et) were prepared and tested for anticonvulsant activity in mice by means of the maximal electroshock seizure test. The ED_{50} values were analyzed in terms of hydrophobic (log *P*), electronic (σ_I) and other parameters by regression analysis. The results are essentially the same as those for previously studied *m*- and *p*-substituted benzyl *N*,*N*-dimethylcarbamates ($X\text{-}C_6H_4\text{-}CH_2OCONMe_2$). The activity depended parabolically on log *P* with an optimum log *P* of 1.7, and was negatively correlated with σ_I. It was also found that the potency is reduced when R_1 is an alkyl group or includes a hydrogen-bonding group. Structural requirements for the optimal potency and the aromatic ring contribution to the activity are discussed.

Keywords——structure–activity relationship; carbamate; anticonvulsant activity; optimum hydrophobicity; hydrogen bonding effect; Hansch analysis

Though a variety of drugs are used as anticonvulsants, limited information concerning their structure–activity relationships is available. It was pointed out by several workers[1] that the potency of anticonvulsants, as well as other central nervous system (CNS) drugs, is related to the hydrophobicity of the molecules.

Our previous quantitative structure–activity relationship (QSAR) studies on the anticonvulsant benzyl *N*,*N*-dimethylcarbamates (I) and phenylacetanilides (II) supported this hypothesis:[2] in both cases, the potency depended parabolically on log *P* (*P* stands for the octanol–water partition coefficient) with an optimum log *P* of about 2. It was also found, from



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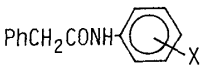

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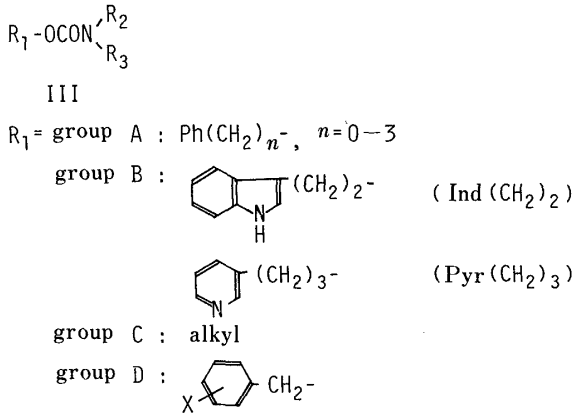

Chart 1

TABLE I. Anticonvulsant Activity and Physicochemical Parameters of Carbamates (III)

No.	Carbamate (III)			$-\log ED_{50}$[a]	log *P*	σ_I[b]	I_A[c]	HB_N[c]	HB_X[c]	HB[c]	Eq. 4		Eq. 6	
	R_1	R_2	R_3								Calcd	Diff.[d]	Calcd	Diff.[d]
	Group A													
1	$PhCH_2$	H	H	3.45	1.22	0.03	0.0	0.0	0.0	0.0	3.66	−0.21	3.63	−0.18
2	$PhCH_2$	H	Me	3.61	1.68	0.03	0.0	0.0	0.0	0.0	3.70	−0.09	3.67	−0.06
3	$PhCH_2$	Me	Me	3.71	2.16	0.03	0.0	0.0	0.0	0.0	3.63	0.08	3.61	0.09
4	$PhCH_2$	Et	Et	3.30	2.93	0.03	0.0	0.0	0.0	0.0	3.31	−0.01	3.35	−0.05
5	$Ph(CH_2)_2$	H	H	3.97	1.50	0.02	0.0	0.0	0.0	0.0	3.74	0.23	3.70	0.27
6	$Ph(CH_2)_2$	Me	Me	3.62	2.40	0.02	0.0	0.0	0.0	0.0	3.60	0.02	3.59	0.03
7	$Ph(CH_2)_2$	Et	Et	3.19	3.20	0.02	0.0	0.0	0.0	0.0	3.17	0.02	3.23	−0.04
8	$Ph(CH_2)_3$	H	H	3.82	1.96	0.01	0.0	0.0	0.0	0.0	3.75	0.07	3.71	0.11
9	$Ph(CH_2)_3$	Me	Me	3.54	2.93	0.01	0.0	0.0	0.0	0.0	3.39	0.15	3.41	0.13
10	$Ph(CH_2)_3$	Et	Et	2.65	3.70[e]	0.01	0.0	0.0	0.0	0.0	2.80	−0.15	2.91	−0.26
11	Ph	Me	Me	3.36	1.69[f]	0.12	0.0	0.0	0.0	0.0	3.34	0.02	3.37	−0.01
12	$PhCH_2(CH_3)CH$	Me	Me	3.39	2.60[g]	0.02	0.0	0.0	0.0	0.0	3.52	−0.13	3.52	−0.13
	Group B													
13	$Ind(CH_2)_2$	H	H	3.44[h]	1.69	0.00[b1]	0.0	1.0	0.0	1.0	3.60	−0.16	3.57	−0.13
14	$Ind(CH_2)_2$	Me	Me	3.38[h]	2.54	0.00[b1]	0.0	1.0	0.0	1.0	3.40	−0.02	3.42	−0.04
15	$Ind(CH_2)_2$	Et	Et	3.09[h]	3.30	0.00[b1]	0.0	1.0	0.0	1.0	2.96	0.13	3.04	0.05
16	$Pyr(CH_2)_3$	H	H	3.30	0.46	0.02[b1]	0.0	1.0	0.0	1.0	3.22	0.08	3.23	0.07
17	$Pyr(CH_2)_3$	Me	Me	3.38	1.44	0.02[b1]	0.0	1.0	0.0	1.0	3.51	−0.13	3.50	−0.12
18	$Pyr(CH_2)_3$	Et	Et	3.49	2.36	0.02[b1]	0.0	1.0	0.0	1.0	3.39	0.10	3.41	0.08
	Group C													
19	Et	H	H	2.71	−0.15[f]	−0.01	1.0	0.0	0.0	0.0	2.59	0.12	2.62	0.09
20	Et	Me	Me	3.05	0.78[f]	−0.01	1.0	0.0	0.0	0.0	3.14	−0.09	3.10	−0.05
21	iso-C_3H_7	Me	Me	3.03	1.38	−0.01	1.0	0.0	0.0	0.0	3.28	−0.25	3.24	−0.21
22	iso-C_4H_9	H	H	3.22	0.98[i]	−0.01	1.0	0.0	0.0	0.0	3.20	0.02	3.16	0.06
23	iso-C_4H_9	Me	Me	3.26	2.00[i]	−0.01	1.0	0.0	0.0	0.0	3.26	0.00	3.23	0.03
24	iso-C_4H_9	Et	Et	2.97	2.82	−0.01	1.0	0.0	0.0	0.0	2.97	0.01	2.98	−0.01
25	$(Et)_2CHCH_2$	H	H	3.41	1.98[i]	−0.01	1.0	0.0	0.0	0.0	3.26	0.15	3.23	0.18
26	$(Et)_2CHCH_2$	Me	Me	3.16	2.87	−0.01	1.0	0.0	0.0	0.0	2.94	0.22	2.96	0.20
27	$(Et)_2CHCH_2$	Et	Et	2.23	3.60[g]	−0.01	1.0	0.0	0.0	0.0	2.41	−0.18	2.51	−0.28

	Group D X (R_1 = X-$C_6H_4CH_2$)											
28	*p*-Me	H	H	3.51	1.76	0.02[b2]	0.0	0.0	0.0	0.0	3.70	−0.19
29	*p*-Me	Me	Me	3.58[j]	2.63[j]	0.02[b2]	0.0	0.0	0.0	0.0	3.51	0.07
30	*p*-Cl	H	H	3.71	1.97	0.05[b2]	0.0	0.0	0.0	0.0	3.58	0.13
31	*p*-Cl	H	Me	3.54	2.42	0.05[b2]	0.0	0.0	0.0	0.0	3.48	0.06
32	*p*-Cl	Me	Me	3.35[j]	2.93[j]	0.05[b2]	0.0	0.0	0.0	0.0	3.28	0.07
33	*m*-Cl	Me	Me	3.41[j]	2.82[j]	0.06[b2]	0.0	0.0	0.0	0.0	3.30	0.11
34	*p*-F	Me	Me	3.50[j]	2.30[j]	0.03[b2]	0.0	0.0	0.0	0.0	3.58	−0.08
35	*p*-Br	Me	Me	3.15[j]	3.01[j]	0.05[b2]	0.0	0.0	0.0	0.0	3.24	−0.09
36	*p*-I	Me	Me	3.14[j]	3.32[j]	0.04[b2]	0.0	0.0	0.0	0.0	3.09	0.05
37	*p*-CF_3	Me	Me	3.10[j]	3.08[j]	0.07[b2]	0.0	0.0	0.0	0.0	3.13	−0.03
38	*m*-OMe	Me	Me	3.49[j]	2.09[j]	0.04[b2]	0.0	0.0	1.0	1.0	3.40	0.09
39	*p*-OMe	Me	Me	3.46[j]	2.20[j]	0.01[b2]	0.0	0.0	1.0	1.0	3.48	−0.02
40	*m*-NH_2	Me	Me	3.45[j]	1.06[j]	0.02[b2]	0.0	0.0	1.0	1.0	3.44	0.01
41	*m*-NMe_2	Me	Me	3.29[j]	2.28[j]	0.02[b2]	0.0	0.0	1.0	1.0	3.43	−0.14
42	*m*-O-iso-C_3H_7	Me	Me	3.21[j]	2.80[j]	0.04[b2]	0.0	0.0	1.0	1.0	3.18	0.03
43	*p*-OCH_2Ph	Me	Me	3.19[j]	3.27[j]	0.00[b2]	0.0	0.0	1.0	1.0	3.06	0.13
44	*p*-NO_2	Me	Me	3.19[j]	1.95[j]	0.08[b2]	0.0	0.0	1.0	1.0	3.29	−0.10
45	*p*-CN	Me	Me	3.16[j]	1.67[j]	0.08[b2]	0.0	0.0	1.0	1.0	3.31	−0.15
46	*m*-OPh	Me	Me	2.92[j]	3.55[j]	0.05[b2]	0.0	0.0	1.0	1.0	2.70	0.22

a) ED_{50}, mol/kg. *b*) Taken from ref. 7 unless otherwise noted. b_1) Estimated from data for closely related compounds. b_2) Calculated value, see the text. *c*) See the text. *d*) Difference between observed values and calculated values. *e*) The value was estimated from data for closely related compounds. *f*) Taken from C. Hansch and A. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology." Wiley-Interscience, New York, 1979. *g*) Determined by high-performance liquid chromatography. See the text. *h*) Unpublished data. *i*) Determined by gas chromatography. See the text. *j*) Taken from our previous paper.[2a]

regression analyses, that the carbamoyl moiety responsible for the anticonvulsant activity can be activated by introducing electron-donating substituents X, and that hydrogen-bonding substituents X in (I) reduce the potency, whereas they do not in (II).

We wanted to know whether these conclusions could be generalized for carbamates with other structures and how the presence of an aromatic ring in the molecule would contribute to the activity. We therefore extended our study to a series of carbamates (III), in which an aromatic group, if present, is located at a variable distance from the amide center.

This paper reports the anticonvulsant activity data of carbamates (III) evaluated in mice by means of the maximal electroshock seizure (MES) test, and the results of their Hansch analysis.[3] Structural requirements to increase the potency are discussed.

Materials and Methods

Carbamates (III)——Carbamates (R_1OCONH_2) were prepared by treating an appropriate alcohol with sodium cyanate in the presence of trifluoroacetic acid according to the method described for the synthesis of *tert*-butyl carbamates.[4] The preparation of *N*-substituted carbamates followed the procedures previously described.[2a] Structures were identified by nuclear magnetic resonance (NMR) spectral (Varian, XL-200 spectrometer), mass spectral (Hitachi, M-80 mass spectrometer) and elemental analyses.

Partition Coefficient——Partition coefficients were determined in the octanol–water system by the usual shaking-flask method.[5] When a compound was insensitive to ultraviolet (UV) spectrophotometry, the concentrations were determined by gas chromatography (Shimadzu, GC-9A gas chromatograph). For the samples whose $\log P$ is too high to be determined by the above-mentioned methods, high-performance liquid chromatography was used, assuming a linear relation between $\log P$ and the capacity factor, $\log k'$.[6] The experimental conditions are the same as those reported in our previous paper.[6]

Anticonvulsant Activity——The ED_{50} values (mol/kg) evaluated from the MES test results were used as an index of anticonvulsant activity. The test compounds were dissolved in sesame oil and injected intraperitoneally 15 min prior to electroshock. The procedures were previously described in detail.[2a]

Correlation Analysis——As described in previous papers,[2] the ED_{50} values were analyzed in terms of hydrophobic ($\log P$), electronic (σ), and additional (E_i) parameters by the least-squares method (Eq. 1).

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

The σ_I values[7] were used to describe the electronic properties of the R_1 group in III (Table I). The following parameters were used as indicator variables in this study.

$I_A = 1$ when R_1 in III is an alkyl group without an aromatic ring,
otherwise $I_A = 0$,
$HB_N = 1$ when the R_1 group has an indole or pyridine ring,
otherwise $HB_N = 0$,
$HB_X = 1$ when carbamate (I) has a hydrogen-bonding substituent X,
otherwise $HB_X = 0$,
$HB = 1$ when the aromatic ring in R_1 in III includes
hydrogen-bonding substituents or hetero atoms in the ring,
otherwise $HB = 0$.

Results and Discussion

The compounds and parameters used in this work are listed in Table I. Regression equations derived for the data set of groups A—B and A—C and the entire data set are summarized in Table II together with related statistical values. The correlations between the parameters used in the final equation are given in Table III.

Aralkyl Carbamates (Groups A and B)

The plot of $-\log ED_{50}$ values against $\log P$ gave a parabolic curve for compounds of group A. The points for all compounds of group B, however, showed downward deviations from this curve. Taking into account that indole and pyridine rings have a hydrogen-bonding amino nitrogen atom, the hydrogen-bonding parameter HB_N was tried. The use of σ_I and HB_N

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

$$-\log ED_{50} = -k(\log P)^2 + k'(\log P) + \rho\sigma_I + \alpha I_A + h_N HB_N + \text{const.}$$

Group	k	k'	ρ	α	h_N	const.	log P_0[a]	n[b]	r[c]	s[d]	$F_{m,n-m-1}$[e]	Eq. no.
A, B	0.231	0.764	−3.876[f]		−0.213[f]	3.179	1.65	18	0.906	0.146	14.89	2
	(0.092)[g]	(0.412)	(3.237)		(0.174)	(0.471)						
A, B, C	0.236	0.839	2.238		0.045	2.735		27	0.800	0.239	9.80	3
	(0.092)	(0.367)	(3.823)		(0.230)	(0.344)						
	0.224	0.723	−3.971[f]	−0.566	−0.221[f]	3.234	1.61	27	0.934	0.146	28.85	4
	(0.056)	(0.228)	(3.128)	(0.190)	(0.167)	(0.269)						

$$-\log ED_{50} = -k(\log P)^2 + k'(\log P) + \rho\sigma_I + \alpha I_A + h_N HB_N + h_X HB_X + \text{const.} \quad \text{or}$$

$$-\log ED_{50} = -k(\log P)^2 + k'(\log P) + \rho\sigma_I + \alpha I_A + hHB + \text{const.}$$

Group	k	k'	ρ	α	h_N	h_X	h	const.	log P_0[a]	n[b]	r[c]	s[d]	$F_{m,n-m-1}$[e]	Eq. no.
A, B, C, D	0.196	0.645	−3.447	−0.554	−0.212	−0.185		3.241	1.65	46	0.913	0.135	32.51	5
	(0.044)	(0.190)	(1.932)	(0.148)	(0.139)	(0.108)		(0.226)						
	0.196	0.648	−3.331	−0.547			−0.194	3.233	1.65	46	0.913	0.134	39.87	6
	(0.044)	(0.188)	(1.785)	(0.142)			(0.093)	(0.218)						

a) Optimum log P value. *b*) Number of points used for calculations. *c*) Correlation coefficient. *d*) Standard deviation. *e*) F value of the correlation; m stands for the number of parameters; Eq. 2; $F_{4,13:\alpha=0.005}=6.23$, Eq. 3; $F_{4,22:\alpha=0.005}=5.02$, Eq. 4; $F_{5,21:\alpha=0.005}=4.68$; $F_{1,21}=38.40$ ($F_{1,21:\alpha=0.005}=9.83$), Eq. 5; $F_{6,39:\alpha=0.005}=3.8$, Eq. 6; $F_{5,40:\alpha=0.005}=3.99$. *f*) Justified at the 97.5% by t-test; the other terms of Eqs. 2, 4, 5 and 6 are justified >99.5%. *g*) Figures in parentheses are 95% confidence intervals.

TABLE III. Simple Correlation Matrix for the Parameters of Eq. 6

	log P	$(\log P)^2$	σ_I	I_A	HB
log P	1.000				
$(\log P)^2$	0.964	1.000			
σ_I	0.109	0.040	1.000		
I_A	−0.252	−0.172	−0.591	1.000	
HB	−0.053	−0.064	0.068	−0.343	1.000

in addition to log P resulted in Eq. 2 as the best correlation, where each term is justified at better than the 97.5% level of significance by the t-test. An attempt to examine the effects of the N-substituents (R_2 and R_3) with the aid of indicator variables led to no significant correlation, indicating that electronic and/or steric effects associated with the N-substituents cause little change in the potency when R_2 and R_3 are methyl or ethyl groups.

Aralkyl and Alkyl Carbamates (Groups A, B, and C)

Examination of the activity data revealed that activities for alkyl carbamates (group C) are much lower than those for the other groups. Thus the analysis using the same parameters as in Eq. 2 gave a poor correlation in Eq. 3. The introduction of the indicator variable I_A to distinguish alkyl carbamates from others improved the correlation to produce Eq. 4, where all terms are significant, judging from the F-test and t-test (Table II). It can be seen that the coefficients of each term in Eq. 4 are much the same as those in Eq. 2.

All Carbamates (Groups A, B, C, and D)

We previously formulated the following equation (Eq. 7) for the anticonvulsant activity of m- and p-substituted benzyl N,N-dimethylcarbamates (I),

$$-\log ED_{50} = -0.209(\log P)^2 + 0.761(\log P) - 0.316\sigma^0 - 0.179HB_X + 2.952 \quad (7)$$
$$(0.074) \quad (0.395) \quad (0.167) \quad (0.114) \quad (0.536)$$
$$n=18, \quad r=0.951, \quad s=0.099$$

where n is the number of compounds, r is the correlation coefficient, s is the standard deviation and the figures in parentheses are 95% confidence intervals. Since the ED_{50} values were evaluated under the same conditions as in the present work, we attempted to combine Eqs. 4 and 7. As shown in Table I, substituted benzyl carbamates were classified as group D, which includes some new data for related compounds. The σ_I values for substituted benzyl groups ($X\text{–}C_6H_4CH_2\text{–}$) were estimated by multiplying σ_I values for $X\text{–}C_6H_4$, available from a linear correlation with Hammett's σ, by the ratio of the ρ values for the dissociation constants of phenylacetic to benzoic acids ($\rho_{X-C_6H_4CH_2CO_2H}/\rho_{X-C_6H_4CO_2H}=0.56$) (Table I).

Regression analyses on the combined data set (groups A—D) with the independent use of HB_N and HB_X gave Eq. 5 as the best correlation. It is interesting to note that the coefficients of HB_N and HB_X are very close. We therefore combined the two parameters HB_N and HB_X into a single hydrogen-bonding parameter, HB, obtaining Eq. 6 (Tables I and II). Equation 6 seems to be equivalent to Eq. 5 in the coefficients of each term as well as the statistics, suggesting that the hydrogen-bonding effects of the R_1 group in carbamates (III) could be described by the common parameter HB. Here again, the substituent effects of R_2 and/or R_3 were found to be statistically insignificant. Thus, we obtained Eq. 4 for groups A—C and Eq. 6 for groups A—D. The $-\log ED_{50}$ values calculated with Eqs. 4 and 6 are included in Table I. The plots based on Eq. 6 are shown in Fig. 1.

Greater residuals observed for the highly lipophilic compounds **10** and **27** may be attributed in part to underestimation of the log P values. The potency of the most active

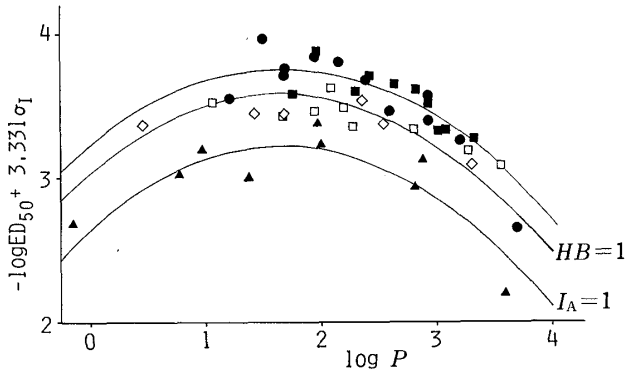

Fig. 1. Relationship between Anticonvulsant Activity (Corrected for the Electronic Parameter (σ_I)) and log P

Lines represent plots based on Eq. 6. ●, group A, $HB=0$; ◇, group B, $HB=1$; ▲, group C, $HB=0$, $I_A=1$; ■, group D, $HB=0$; □, group D, $HB=1$.

compound, **5**, is higher than expected. The reason for this is not clear at present.

Based on the QSAR results, the structural requirements for the optimal potency can be summarized as follows. (1) Hydrophobicity close to log $P \simeq 1.7$ is preferred. (2). The R_1 group should be electron-donating since the negative ρ_I (-3.33) requires substituents of negative σ_I for a positive contribution to the activity. (3) The R_1 group should have neither a hydrogen-bonding aromatic substituent nor a heterocyclic ring, since a negative coefficient of HB means that such hydrogen bonders reduce the activity. (4) When R_1 is an alkyl group, the activity is enormously reduced. Introduction of a phenyl ring is thought to play an important role in enhancing the activity. Such activity-enhancement effects are independent of the distance between the phenyl ring and the reaction center.

Among these, the requirements (1)—(3) are consistent with those obtained for carbamates (I).[2a] The magnitude of the contribution made by the phenyl ring to the anticonvulsant activity may be estimated to be 0.55 in log units as shown by the regression coefficient of the I_A term, that is, the involvement of the phenyl ring in the R_1 group, regardless of its location, produces an increase of the ED_{50} value by 3.5 times, with other conditions constant. It should be noted, however, that heterocyclic aromatic rings (classified as B group) are not as effective as a phenyl ring because the activity-enhancing aromatic effects are partly cancelled out by the activity-reducing hydrogen-bonding effects.

The characteristic behavior associated with the aromatic component seems to be suggestive of the involvement of important π-electron interactions with the bio-phase in the critical process.

Our experiments did not reveal any steric requirements around the carbamoyl moiety (*i.e.* reaction center). In order to identify a desirable substitution pattern on the amide nitrogen, it would be necessary to examine compounds having bulkier *N*-substituents than the ethyl group we used.

There are only two compounds, **12** and **21**, which have a branching at the C_α-position (C_α refers to the carbon atom adjacent to the OCON=group) in R_1. The observed potencies for these compounds are both lower than the predicted values. Though two data points are not sufficient to discuss the steric effects of the α-branching structure, this does suggest that such α-branching effects, if any, would reduce the activity.

In conclusion, we have formulated Eq. 6 for the anticonvulsant activity of carbamates (III). The structural requirements for the optimal potency are essentially the same as those previously obtained for substituted benzyl carbamates (I).[2a] With these results in mind, we are looking for a new type of amide-containing anticonvulsant of higher potency.

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