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A Quantitative Structure-Activity Study of Anticonvulsant Benzyl *N,N*-Dimethylcarbamates

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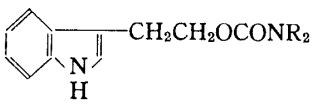
A series of *m*- and *p*-substituted benzyl *N,N*-dimethylcarbamates was prepared then evaluated for anticonvulsant activity in mice by means of the maximal electroshock seizure test. The ED_{50} value correlated well with the hydrophobic (log *P*, 1-octanol–H_2O partition coefficient), electronic (σ°) and hydrogen bonding (HB) characters of the tested compounds on regression analyses. The relative activity depended parabolically on log *P*; the optimum value of hydrophobic character (log P_0) was 1.82. This agrees well with values found empirically for central nervous system depressants (log $P_0 \simeq 2$). Electron-donating substituents enhanced the activity, an indication of interaction between the carbamoyl moiety and an acidic group on the receptor site. Hydrogen bond-accepting ability of the substituent reduced anticonvulsant activity, while non-hydrogen bonders did not. The overall substituent effects were such that the activity of the unsubstituted compound was almost optimum.

Keywords——structure–activity relationship; Hansch analysis; benzylcarbamates; anticonvulsant activity; optimum hydrophobicity; substituent electronic effect; hydrogen bonding effect

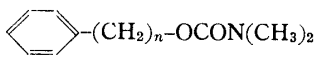
Tryptophol (indole-3-ethanol), a metabolite of tryptophan, produces a hypnotic effect.[1] This fact prompted us to study the actions of tryptophol derivatives on the central nervous system (CNS). We found that its carbamates such as **1** have pronounced anticonvulsant action in mice,[2] which was to be expected as the conversion of alcohol into carbamates often results in the enhancement of anticonvulsant activity.[3] Further studies showing that *β*-phenethyl *N,N*-dimethylcarbamate (**2**, $n=2$) had a similar, or somewhat greater potency, indicated that the structure which produces this activity is not the indole nucleus but the carbamoyl moiety. This finding is consistent with the fact that many anticonvulsants used in central nervous system disorders have one or more –CON= groups. We also examined analogous aralkyl *N,N*-dimethylcarbamates (**2**, $n=0$—3) and found benzyl *N,N*-dimethylcarbamate (**3**, X=H) to be the most potent, *i.e.*, about three times more potent than mephenesin (**4**).

In the work reported here, new *m*- and *p*-substituted benzyl *N,N*-dimethylcarbamates (**3**) were prepared and were tested for anticonvulsant activity by means of the maximal electroshock seizure (MES) test. The substituent effects on relative activities were quantitatively



R=H, CH_3, C_2H_5

1



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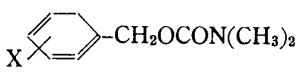

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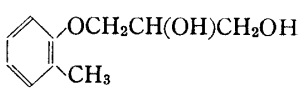

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Chart 1

separated into hydrophobic (log P, (log P)^2), electronic (σ°) and hydrogen bonding (HB) factors by Hansch analysis. Structural requirements for maximal potency derived from the correlation equation are also given.

Table I. Anticonvulsant Activity and Physicochemical Parameters of Substituted Benzyl *N,N*-Dimethylcarbamates

No.	X	log$P$	σ^{0} [b]	HB	−log ED_{50} [a] Obsd.	−log ED_{50} [a] Calcd[c]	Diff.[d]
3a	H	2.16	0.00	0.00	3.71	3.62	0.09
3b	*p*-CH_3	2.63	−0.15	0.00	3.58	3.56	0.02
3c	*p*-F	2.30	0.17	0.00	3.50	3.54	−0.04
3d	*m*-OCH_3	2.09	0.13	1.00	3.49	3.41	0.08
3e	*p*-OCH_3	2.20	−0.12	1.00	3.46	3.47	−0.01
3f	*m*-NH_2	1.06	−0.14	1.00	3.45	3.39	0.06
3g	*m*-Cl	2.82	0.37	0.00	3.41	3.32	0.09
3h	*p*-Cl	2.93	0.27	0.00	3.35	3.30	0.05
3i	*m*-$N(CH_3)_2$	2.28	−0.15	1.00	3.29	3.47	−0.18
3j	*m*-O-iso-Pr	2.80	0.04[e]	1.00	3.21	3.25	−0.04
3k	*p*-OCH_2Ph	3.27	−0.42[f]	1.00	3.19	3.16	0.03
3l	*p*-NO_2	1.95	0.82	1.00	3.19	3.20	−0.01
3m	*p*-CN	1.67	0.69	1.00	3.16	3.24	−0.08
3n	*p*-Br	3.01	0.26	0.00	3.15	3.27	−0.12
3o	*p*-I	3.32	0.27	0.00	3.14	3.09	0.05
3p	*p*-CF_3	3.08	0.53[g]	0.00	3.10	3.15	−0.05
3q	*m*-OPh	3.55	0.25[f]	1.00	2.92	2.76	0.16
3r	*p*-*tert*-Bu	4.14[h]	−0.17[g]	0.00	2.47	2.57	−0.10
3s	*p*-$OCON(CH_3)_2$[i]	1.59	0.17[j]	1.00	3.09	3.40	−0.31
3t	*p*-SCH_3[i]	2.12	0.08[g]	1.00	2.88	3.42	−0.54

a) ED_{50}, mol/kg. *b*) Taken from R.W.Taft, *J. Phys. Chem.*, **64**, 1805 (1960) unless otherwise noted. *c*) Calculated from eq.5. *d*) Diff, the difference between observed and calculated values. *e*) Estimated from data for closely related substituents. *f*) Approximated by the σ value from ref 15*a*. *g*) Taken from O. Exner, "Advances in Linear Free Energy Relationships", N.B. Chapman and J. Shorter, Eds., Plenum Press, London 1972 p. 27. *h*) Calculated as follows; log P (**3a**) + π (*tert*-Bu) = 2.16 + 1.98 = 4.14. The π value for *tert*-Bu was taken from ref. 15*a*. *i*) Omitted from the calculation. *j*) Calculated as follows; $\sigma_{OCON(CH3)2} = \sigma_{OCOCH3} - \sigma_{COCH3} + \sigma_{CON(CH3)2} = 0.31 - 0.50 + 0.36 = 0.17$. σ_{OCOCH3} and δ_{COCH3} were taken from ref. 15*a* and $\sigma_{CON(CH3)2}$ was estimated from data for closely related substituents.

Table II. Physical Properties and Anticonvulsant Activity of Substituted Benzyl *N,N*-Dimethylcarbamates

No.	Formula[a]	Method[b]	Yield[c] (%)	bp (mmHg)[d] or mp (°C)	MS, *m/e* M$^+$	IR ($CHCl_3$) ν, cm^{-1}	^1H NMR ($CDCl_3$) δ, ppm	ED_{50} (95% confidence limits) μmol/kg
3a	$C_{10}H_{13}NO_2$	A	58	115(5)	179	1690	2.93 (s, 6, $N(CH_3)_2$), 5.13 (s, 2, $ArCH_2$), 7.35 (s, 5, ArH)	195(163—233)
3b	$C_{11}H_{15}NO_2$	A	73	Oil	193	1690	2.33 (s, 3, CH_3), 2.92 (s, 6, $N(CH_3)_2$), 5.09 (s, 2, $ArCH_2$), 7.0—7.4 (4, ArH)	264(240—291)
3c	$C_{10}H_{12}FNO_2$	A	48	Oil	197	1700	2.93 (s, 6, $N(CH_3)_2$), 5.09 (s, 2, $ArCH_2$), 6.8—7.5 (4, ArH)	320(262—390)
3d	$C_{11}H_{15}NO_3$	B	37	Oil	209	1700	2.92 (s, 6, $N(CH_3)_2$), 3.80 (s, 3, OCH_3), 5.10 (s, 2, $ArCH_2$), 6.7—7.4 (4, ArH)	326(273—390)
3e	$C_{11}H_{15}NO_3$	A	70	Oil	209	1695	2.90 (s, 6, $N(CH_3)_2$), 3.78 (s, 3, OCH_3), 5.04 (s, 2, $ArCH_2$), 7.08 (ABq, J = 9, 4, ArH)	344(306—387)

No.	Formula[a]	Method[b]	Yield[c] (%)	bp (mmHg)[d] or mp (°C)	MS, *m/e* M^+	IR ($CHCl_3$) ν, cm^{-1}	^1H NMR ($CDCl_3$) δ, ppm	ED_{50} (95% confidence limits) μmol/kg
3f	$C_{10}H_{14}N_2O_2$	B	70	51—52	194	1700 3370, 3450	2.92 (s, 6, $N(CH_3)_2$), 3.67 (s, 2, NH_2), 5.03 (s, 2, $ArCH_2$), 6.4—7.3 (4, ArH)	358 (311—412)
3g	$C_{10}H_{12}ClNO_2$	A	57	Oil	213	1700	2.95 (s, 6, $N(CH_3)_2$), 5.10 (s, 2, $ArCH_2$), 7.1—7.4 (4, ArH)	390 (345—441)
3h	$C_{10}H_{12}ClNO_2$	A	86	Oil	213	1700	2.92 (s, 6, $N(CH_3)_2$), 5.10 (s, 2, $ArCH_2$), 7.31 (4, ArH)	445 (400—495)
3i	$C_{12}H_{18}N_2O_2$	B		Oil	222	1700	2.95 (s, 12, $CON(CH_3)_2$ and $N(CH_3)_2$), 5.10 (s, 2, $ArCH_2$), 6.6—7.3 (4, ArH)	515 (452—587)
3j	$C_{13}H_{19}NO_3$	B	58	Oil	237	1700	1.33 (d, J = 6, 6, $CH(CH_3)_2$), 2.92 (s, 6, $N(CH_3)_2$), 4.54 (m, J = 6, 1, $CH(CH_3)_2$), 5.09 (s, 2, $ArCH_2$), 6.7—7.4 (4, ArH)	618 (526—726)
3k	$C_{17}H_{19}NO_3$	B	43	40	285	1685	2.88 (s, 6, $N(CH_3)_2$), 5.03 (s, 4, $ArCH_2$ and OCH_2Ar), 6.8—7.4 (4, ArH), 7.33 (s, 5, Ar)	653 (549—777)
3l	$C_{10}H_{12}N_2O_4$	A	35	104—105	224	1710	2.96 (s, 6, $N(CH_3)_2$), 5.22 (s, 2, $ArCH_2$), 7.86 (ABq, J = 8.5, 4, ArH)	640 (571—717)
3m	$C_{11}H_{12}N_2O_2$	A	49	69—70	204	1710 2240	2.98 (s, 6, $N(CH_3)_2$), 5.18 (s, 2, $ArCH_2$), 7.2—7.8 (4, ArH)	700 (645—760)
3n	$C_{10}H_{12}BrNO_2$	A	75	Oil	257	1700	2.98 (s, 6, $N(CH_3)_2$), 5.10 (s, 2, $ArCH_2$), 7.1—7.6 (4, ArH)	710 (623—809)
3o	$C_{10}H_{12}INO_2$	B	42	Oil	305	1705	2.94 (s, 6, $N(CH_3)_2$), 5.08 (s, 2, $ArCH_2$), 7.40 (ABq, J = 8, 4, ArH)	730 (593—898)
3p	$C_{11}H_{12}F_3NO_2$	A	50	Oil	247	1700	2.96 (s, 6, $N(CH_3)_2$), 5.18 (s, 2, $ArCH_2$), 7.2—7.7 (4, ArH)	800 (672—952)
3q	$C_{16}H_{17}NO_3$	B	41	Oil	271	1705	2.93 (s, 6, $N(CH_3)_2$), 5.15 (s, 2, $ArCH_2$), 6.8—7.6 (9, ArH)	1215 (924—1598)
3r	$C_{14}H_{21}NO_2$	B	32	46—47	235	1700	1.32 (s, 9, $C(CH_3)_3$), 2.95 (s, 6, $N(CH_3)_2$), 5.12 (s, 2, $ArCH_2$), 7.2—7.4 (4, ArH)	3400 (2740—4220)
3s	$C_{13}H_{18}N_2O_4$	A	35	76—77	266	1710	2.90 (s, 6, $N(CH_3)_2$), 3.03 (s, 6, $OCON(CH_3)_2$), 5.08 (s, 2, $ArCH_2$), 7.20 (ABq, J = 8.5, 4, ArH)	810 (744—881)
3t	$C_{11}H_{15}NO_2S$	A	53	45—46	225	1700	2.48 (s, 3, SCH_3), 2.92 (s, 6, $N(CH_3)_2$), 5.07 (s, 2, $ArCH_2$), 7.22—7.38 (4, ArH)	1320 (1120—1560)

a) Analyses of all the compounds were within 0.4% of the theoretical values for C.H.N. *b*) See text. *c*) Evaluated after complete purification. *d*) Crystallized from the neat compound.

Materials and Methods

The compounds studied are listed in Table I. Substituents were chosen so as to cover a wide range of hydrophobic and electronic characters. The carbamates, **3a**—**t**, were prepared by treating the corresponding benzyl alcohol (**5**) with *N*,*N*-dimethylcarbamoyl chloride in pyridine (method A) or in the presence of NaH in benzene (method B). (In the preparation of **3s**, *p*-hydroxybenzyl alcohol was used as the starting material.) All but the unsubstituted (**3a**) derivatives are new compounds. Structural assignments were verified by

nuclear magnetic resonance (NMR) (Varian A-60D; tetramethylsilane (TMS) as the internal standard), infrared (IR) (Hitachi 295 infrared spectrometer), mass (MS) (JEOL JMS-01SG mass spectrometer) and elemental analyses. Analytical results were within $\pm 0.4\%$ of the theoretical values for C, H and N. Physical properties and experimental conditions (method A or B) are shown in Table II. The preparation procedure for benzyl alcohols and the general method for preparing carbamates were as follows.

Benzyl Alcohols——*p*-Trifluoromethylbenzyl and *p*-methylthiobenzyl alcohols (**5p** and **5t**) were prepared according to the established methods.[4,5] *p*-Cyanobenzyl alcohol (**5m**) was obtained from the corresponding aldehyde by conventional $NaBH_4$ reduction. *m*-Isopropoxybenzyl alcohol (**5j**) was prepared by treating potassium *m*-hydroxymethylphenoxide with isopropyl iodide in methanol (Williamson synthesis). *p*-Iodobenzyl alcohol (**5o**) was prepared from *p*-aminobenzyl alcohol by the method described for the preparation of iodobenzene from aniline.[6] Preparation of *m*-dimethylaminobenzyl alcohol (**5i**) followed the procedure of Giumanini and his co-workers for synthesizing dimethylaminobenzene.[7] The other benzyl alcohols were obtained commercially.

Carbamates 3a—c, 3e, 3g, 3h, 3l—n, 3p, 3s, and 3t. General Method A——A mixture of *N*,*N*-dimethylcarbamoyl chloride (16 mmol) and the appropriate substituted benzyl alcohol (8 mmol) in pyridine (2.5 ml) was stirred under reflux for 3 h. After cooling of the reaction mixture, it was taken up in benzene and 5% HCl solution. The organic layer was washed thoroughly with H_2O, then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

Carbamates 3d, 3f, 3i—k, 3o, 3q, and 3r. General Method B——Fifty percent NaH (9 mmol) was added to a stirred solution of the appropriate benzyl alcohol (8 mmol) in dry benzene (4 ml), then *N*,*N*-dimethylcarbamoyl chloride (9 mmol) was added. The reaction mixture was refluxed for 1 h, then diluted with benzene. The benzene solution was washed with H_2O and dried, then the solvent was removed. The residue was purified by silica gel column chromatography.

Correlation Analysis——Relationships between biological activity and physicochemical parameters can be examined by fitting the parameters to eq. 1,[8]

$$\log(1/C) = k'(\log P) - k(\log P)^2 + \rho\sigma + \sum e_i E_i + \text{const} \qquad (1)$$

where C is the molar concentration of drug causing a standard biological response, $\log P$ (P represents the 1-octanol–H_2O partition coefficient) and σ are the hydrophobic and electronic parameters, and E_i represents other effects such as steric and hydrogen bonding. The intercept, k, k', ρ and e_i are constants determined by the least-squares method. Anticonvulsant activity is expressed as $\log(1/ED_{50})$, from the ED_{50} values (mol/kg) in mice evaluated by the MES method. As the electronic parametr, σ° for the insulated substituent effect was used. As described later, only the hydrogen-bonding indicator variable (HB) was significant among the additional parameters, E_i. The parameter HB takes the values 0 for non-hydrogen bonders and 1 for hydrogen acceptors. All the parameters used are summarized in Table I. Regression analyses were performed with a FACOM 230/75 computer at the Data Processing Center of Kyoto University.

Partition Coefficients——Partition coefficients for benzyl *N*,*N*-dimethylcarbamates were determined by the usual shaking method.[9] The concentration in the water phase was measured spectrophotometrically (Hitachi, 220 spectrometer). Determinations were performed for at least three different concentrations. The results are given in Table I. For **3r** the calculated value was used (see footnote to Table I) because the P value is too high to be determined exactly.

Anticonvulsant Activity——Male ddY strain mice weighing 21—24 g were kept in an air-conditioned room (24 ± 1°C, $55 \pm 5\%$ humidity) lighted for 12 h a day (6: 30 to 18: 30). The test compounds were dissolved in sesame oil and injected intraperitoneally (0.1 ml/10 g body weight) 15 min prior to electroshock. The ability of a compound to prevent the tonic extensor convulsion (TE) phase of MES evoked by supramaximal current (a 50 mA, 0.2 s stimulus through corneal electrodes) was evaluated. The ED_{50} values and 95% confidence limits were calculated by the method of Litchfield and Wilcoxon.[10] Six to 12 mice were used for each dose. The purity of the compounds was checked by thin-layer chromatography (TLC) just before the pharmacological measurements. The results are shown in Table II. Attempts to estimate the ED_{50} values for compounds having a hydrophilic substituent, such as $CONH_2$ or NHAc, failed due to their limited solubility in sesame oil.

Results and Discussion

Equations obtained by regression analyses from the data in Table I are listed in Table III together with some statistical values. Correlations between the parameters used are insignificant as shown in Table IV. Taking account of the substrate structure **3**, in which no direct conjugative interaction between the aromatic system and the carbamoyl group can occur, we selected the electronic parameter, σ°, instead of σ, though equivalent correlations were obtained with σ ($s=0.130$, $r=0.907$ for eq. 4, and $s=0.101$, $r=0.949$ for eq. 5). Compounds **3s** and **3t**

are not included in these analyses, for a reason which will be described later. The levels of significance for all the correlations are better than 99.5%, based on the results of the F test. Each term is justified at the 99.5% level by the t test, except for the log P term in eq. 3 and the σ° term in eq. 4, both of which are justified at the 97.5% level by the t test. The calculated log $(1/ED_{50})$ values in Table I were obtained with eq. 5.

The best correlation (eq. 5) shows a parabolic dependence on log P, as in the cases of many other CNS drugs.[11] The optimum hydrophobic character (log P_0) calculated from eq. 5 is 1.82, which is very close to the value reported for anticonvulsant activity in rats (log P_0= 1.70)[11c] and for the hypnotic activity of barbiturates (log P_0=2).[11a] This value, 1.82, is also close to the log P_0 value of benzeneboronic acids, 2.3, estimated for penetration into mouse brain.[11a] Hence, the log P_0 value for our series 3 is probably determined mainly by the penetration process into the brain, although in part it is controlled by hydrophobic interaction with receptor sites.

Table III. Sequential Development of the Correlation Equation for the Anticonvulsant Activity of Benzyl *N,N*-Dimethylcarbamates

$$-\log ED_{50} = k' (\log P) - k (\log P)^2 + \rho\sigma^\circ + h\mathrm{HB} + \text{const.}$$

k'	k	ρ	h	Const.	n[a]	s[b]	r[c]	$F_{1,x}$[d]	Eq. No.
−0.255				3.934	18	0.214	0.671	13.13	(2)
(0.149)[e]				(0.406)					
0.797	0.202			2.668	18	0.158	0.850	14.60	(3)
(0.597)	(0.113)			(0.767)					
0.901	0.225	−0.281		2.611	18	0.131	0.906	7.73	(4)
(0.505)	(0.096)	(0.217)		(0.643)					
0.761	0.209	−0.316	−0.179	2.952	18	0.099	0.951	11.46	(5)
(0.395)	(0.074)	(0.167)	(0.114)	(0.536)					

a) Number of points used for correlations. *b*) Standard deviation. *c*) Correlation coefficient. *d*) $F_{1,16;\alpha=0.005}$ = 10.58, $F_{1,18;\alpha=0.005}$ = 10.80, $F_{1,14;\alpha=0.025}$ = 6.30, $F_{1,13;\alpha=0.05}$=11.37. *e*) Figures in parentheses are 95% confidence intervals.

Table IV. Simple Correlation Matrix for the Parameters of Equations 2—5

	log$P$	$(\log P)^2$	σ^0	HB
log P	1.00	0.98	−0.15	−0.43
$(\log P)^2$		1.00	−0.19	−0.39
σ^0			1.00	−0.08
HB				1.00

The negative value of ρ in eq. 5 means that an electron-donating substituent is favored to enhance activity. The $\rho\sigma$ term in correlation equations should provide useful information about the action mechanism.[12] The negative ρ value suggests interaction with an electron-deficient center on the receptor site. The absolute value, 0.32, is close to that observed for the alkaline hydrolysis of ethyl substituted-phenylpropionates, 0.49,[13] an indication that electron migration from the amide group may be involved in this interaction.

The HB term in eq. 5 means that substituents lacking hydrogen-bonding ability are preferred to hydrogen acceptors. The coefficient of the HB term has recently been shown to correspond to the molarity ratio of the hydrogen donor groups contained in the biological phase and in the 1-octanol used as the reference for the hydrophobic phase.[14] The involvement of hydrophobic interaction in the critical process at the target results in a linear correlation with log P (included in k' in eq. 1); whereas, drug movement through a number of barriers to

the target phase is described by the parabolic model. Hence, the 1st order HB term in eq. 5 reflects the hydrogen-bonding effect in the hydrophobic binding process of the test compound onto the receptor site rather than the process of its transport to the central nervous system. The negative coefficient suggests that a hydrogen donor group with a molarity lower than that of 1-octanol exists in the lipophilic biophase surrounding the receptor.

On the basis of the above discussion, the structural requirements for maximum potency are as follows: (a) log $P \simeq 1.82$ ($\pi = -0.3$, where π is the hydrophobic constant defined by $\pi_x = \log P_x - \log P_H$) and a substituent on the benzene ring which should be (b) electron donating and (c) non-hydrogen bonding. It is difficult to find substituents which satisfy both (a) and (c) because most substituents with negative π generally possess one or more hetero atoms capable of hydrogen bonding. As to the electronic factor, (b), the introduction of an electron-donating group seems to destabilize compounds. For example, substitutions with a powerful electron donor, such as the *p*-NH_2 or *p*-$N(CH_3)_2$ group, were unsuccessful because of rapid decomposition of the substituted compounds during purification. The unsubstituted compound, **3a** (non-hydrogen bonder), has almost ideal hydrophobicity (log $P = 2.12$, compared with log $P_0 = 1.82$), so further attempts to find congeners with higher activity than **3a** by modifying the aromatic substituent are unlikely to be fruitful.

The ED_{50} values for **3t** is poorly predicted by eq. 5 probably because of the *in vivo* oxidation of the SCH_3 group. By assuming that SCH_3 is oxidized to $SOCH_3$, or SO_2CH_3, and taking into account the parameters given in the literature (for $SOCH_3$, $\pi = -1.58$, $\sigma^\circ = 0.57$ and for SO_2CH_3, $\pi = -1.63$, $\sigma^\circ = 0.75$),[15] we obtained calculated log ($1/ED_{50}$) values of 2.96 ($SOCH_3$) and 2.88 (SO_2CH_3) with eq. 5. Both values agree well with the observed value of 2.88, in accord with our reasoning.

We have yet to ascertain why **3s** deviates from the expected relationship. Since phenyl carbamates are known to react with cholinesterase,[12] **3s** may be consumed before reaching the target site for the anti-electroshock seizure activity. An investigation of this possibility is in progress.

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