Structural Requirements for Centrally Acting Drugs I

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Abstract □ Various CNS activities, such as antielectroshock, antipentylenetetrazol-induced seizures, muscle relaxant, and acute lethal toxicity, of different types of compounds were correlated with three physicochemical parameters, namely lipophilicity (log P), dipole moment, and steric considerations (E_s). The relatively narrow range of log P_0 (2.0 ± 0.7) for compounds possessing a polar group, *e.g.*, amido, thioamido, keto, or alcoholic function, strongly suggests that the rate-limiting step for these different CNS-acting drugs is probably the same, namely the penetration of the tightly packed neuroglial cells (the so-called blood–brain barrier). Negative dependence of the anticonvulsant or CNS depressant activity on the dipole moment and positive dependence of the stimulatory CNS toxicity on the same parameter were found to be statistically significant. Entirely different sites and mechanisms of action appear to be evident from the very low estimated log P_0 values of lactones and 2-sulfamoylbenzoates for their CNS depressant activities. The CNS activity of five lactones was studied in mice. While γ-butyrolactone caused dosage-dependent sedation and sleep at 100–1000 mg./kg., no loss of the righting reflex was observed for α-methyl-γ-butyrolactone (1000 mg./kg.), γ-valerolactone (2000 mg./kg.), δ-valerolactone (750 mg./kg.), and γ-heptalactone (1000 mg./kg.). After intraperitoneal injection of γ-valerolactone and γ-heptalactone, paralysis of the hind legs was observed, indicating local anesthetic activity on the peripheral nervous system.

Keyphrases □ CNS activity—investigation of structural requirements □ Structure–activity relationships—structural requirements for CNS activity □ γ-Butyrolactone—CNS depressant activity, effect of lipophilicity □ Lipophilicity—relationship to CNS activity

Due to the highly intricate circuitry of the CNS and the very complex interplay of various neurotransmitters, the exact mechanisms of actions of many centrally acting drugs are poorly understood. Since the CNS depressant activity and the degree of depression vary according to the part of the nervous system affected, the overall action may be a summation of several effects. Furthermore, most CNS stimulants or depressants have an action that spreads to other parts of the nervous system, even though the initial action affects only a certain site.

To develop safer and more specific agents for various therapeutic applications, it would be desirable to have some quantitative and qualitative guidelines to assist medicinal chemists in drug design. For example, Hansch *et al.* (1) reported that the ideal log P_0 (octanol–water) for the penetration of the brain by benzeneboronic acids and the ED_{50} of barbiturates is 2.3–2.4.

The sedative–hypnotic effects of γ-butyrolactone and its corresponding open-chain compound, γ-hydroxybutyrate, have been demonstrated in various laboratory animals (2–4). Relatively high dosage levels (100–1000 mg./kg.) of γ-butyrolactone are required to cause dosage-dependent sedation and sleep (4). Although many elegant pharmacological studies have been reported on γ-butyrolactone, few systematic studies have been reported on the structure–activity relationship of its congeners or bioisosteres (5). It has been shown that in many cases the CNS activity of congeneric members increases as the lipophilic character increases until the apex is reached, and then further increase in lipophilic character causes a decrease in activity (6–10). This has been attributed to the ease of random walk of organic molecules. Since γ-butyrolactone has a very low octanol–water partition coefficient (log $P < 0.8$), it is conceivable that its relatively low potency is due to its poor lipoid solubility and limited ability to penetrate through the blood–brain barrier.

The purposes of this paper are to report a number of quantitative structure–activity correlations using various physicochemical parameters, to examine the structural requirements for various types of CNS activity, and to investigate whether the CNS depressant activity of γ-butyrolactone could be enhanced by increasing its lipophilicity.

Table I—Biological Data and Physicochemical Constants Used in the Regression Analysis

Antielectroshock, −log 1/C, moles/kg.		Muscle Relaxant, log 1/C		Acute Lethal Toxicity, log 1/C				
Obs.[a]	Calc.[b]	Obs.[a]	Calc.[c]	Obs.[a]	Calc.[d]	log P	μ[e]	Compound
2.33	2.46	2.04	2.14	1.75	1.88	0.81[f]	3.08	Cyclohexanone
3.02	3.05	2.74	2.68	2.20	2.40	3.62	3.31	2-(2-Tolyl)cyclohexanone
3.24	3.05	2.74	2.81	2.47	2.38	1.71	(3.31)[g]	2-(*p*-Aminophenyl)cyclohexanone
2.95	3.17	2.76	2.94	2.38	2.49	2.62	3.64	2-(α-Hydroxy-*p*-chlorobenzyl)cyclohexanone
3.00	2.71	2.48	2.25	2.48	2.13	4.14	3.31	2-(*p*-Chlorobenzyl)-cyclohexanone
2.92	3.18	2.31	2.52	2.31	2.48	4.31	1.67	α-Cyclohexyl-*p*-chlorobenzyl alcohol
2.92	2.87	—	—	—	—	4.63	1.67	α-Cyclohexyl-*p*-bromobenzyl alcohol
3.90	3.78	3.38	3.30	3.03	2.93	1.42[h]	0.87[h]	Sodium phenobarbital
—	—	2.96	2.79	2.48	2.41	1.41	(2.68)[g]	Mephenesin

Table I—(*Continued*)

Antielectroshock, log 1/C, moles/kg. Obs.	Calc.[i]	log P	μ	Compound
2.16[i]	1.90	−0.37[i]	1.74[i]	Trimethadione
2.59	2.52	0.13	1.69	Paramethadione
3.72	3.60	1.53	1.74	5-Ethyl-5-phenylhydantoin
4.40	3.84	2.47	1.74	Diphenylhydantoin
3.05	3.05	0.70	1.74	5-Phenylhydantoin
3.28	3.32	0.98	1.61	3-Methyl-3-phenylsuccinimide
3.00	3.23	0.65[h]	1.13	Barbital
3.54	3.62	1.48	1.61	3-Ethyl-3-phenylsuccinimide
3.74	3.87	2.25	1.61	3,3-Diphenylsuccinimide
2.77[i]	2.90	0.48[i]	1.61[i]	3-Phenylsuccinimide
2.33[a]	2.65	0.81[f]	3.08[e]	Cyclohexanone
3.02	3.03	3.62	3.31	2-(2-Tolyl)cyclohexanone
3.24	3.10	1.71	(3.31)[g]	2-(*p*-Aminophenyl)-cyclohexanone
2.95	3.15	2.62	3.64	2-(α-Hydroxy-*p*-chlorobenzyl)cyclohexanone
3.00	2.73	4.14	3.31	2-(*p*-Chlorobenzyl)-cyclohexanone
2.92	3.22	4.31	1.67	α-Cyclohexyl-*p*-chlorobenzyl alcohol
2.92	2.95	4.63	1.67	α-Cyclohexyl-*p*-bromobenzyl alcohol
3.90[a]	3.86	1.42[h]	0.87[h]	Sodium phenobarbital

Antipentylenetetrazol-Induced Seizures, —log 1/C, moles/kg.— Obs.[o]	Calc.[p]	log P	μ[q]	Compound
1.07	0.80	1.98	0.87	Mephobarbital
0.97	0.91	2.09	1.74	Mephenytoin
0.01	0.21	1.40	1.61	Phensuximide
0.38	0.35	1.54	1.61	Methsuximide
−1.17	−1.21	0.01	1.47	Ethosuximide

Antipentylenetetrazol-Induced Seizures, —log 1/C, moles/kg.— Obs.[o]	Calc.[q]	Calc.[r]	log P	μ	Compound
0.93	0.59	0.89	1.42[h,i]	0.87[h]	Phenobarbital
0.99	0.71	0.99	1.98	0.87[h]	Mephobarbital
0.69	0.52	0.68	1.21	1.13	Metharbital
0.76	0.72	0.84	2.78	1.13	Phetharbital
0.47	0.72	—	2.10	—	Primidone
0.61	0.72	0.48	2.09	1.74	Mephenytoin
0.73	0.74	—	2.51	—	Albutoin
0.15	0.24	—	0.57	—	Phenacemide
−0.65	−0.39	−0.45	−0.37	1.74	Trimethadione
−0.76	−0.88	−0.87	−0.93	1.74	Dimethadione
0.36	0.58	0.45	1.40	1.61	Phensuximide
0.49	0.62	0.49	1.54	1.61	Methsuximide
0.02	−0.10	−0.05	0.01	1.47	Ethosuximide

Acute Lethal Toxicity, —log 1/C, moles/kg.— Obs.[o]	Calc.[s]	Calc.[t]	log P	μ	Compound
0.61	0.28	0.54	1.42[h,i]	0.87[h]	Phenobarbital
0.58	0.36	0.56	1.98	0.87	Mephobarbital
0.43	0.22	0.40	1.21	1.13	Metharbital
0.14	0.25	0.24	2.78	1.13	Phetharbital
0.35	0.36	0.23	2.09	1.74	Mephenytoin
0.10	0.32	—	2.51	—	Albutoin
−0.56	−0.09	—	0.57	—	Phenacemide
−0.89	−0.86	−0.78	−0.37	1.74	Trimethadione
−1.27	−1.49	−1.39	−0.93	1.74	Dimethadione
0.20	0.28	0.27	1.40	1.61	Phensuximide
0.31	0.31	0.29	1.54	1.61	Methsuximide
−0.45	−0.50	−0.35	0.01	1.47	Ethosuximide
−0.95	−0.75	—	−0.26	—	Acetazolamide
0.43	0.33	—	2.44	—	Chlordiazepoxide
−0.71	—	—	2.10	—	Primidone

Antielectroshock — In Mice — log 1/C, moles/kg. Obs.[k]	Calc.[l]	In Rats — log 1/C, moles/kg. Obs.[k]	Calc.[m]	log P	E_s[n] (R_1)	Compound
2.76	2.57	2.86	2.87	0.58	0.00	1-Methyl-5-α-thienylhydantoin
2.91	2.78	3.13	3.12	1.08	−0.07	1-Ethyl-5-α-thienylhydantoin
2.72	2.87	3.14	3.09	1.58	−0.36	1-*n*-Propyl-5-α-thienylhydantoin
2.94	2.72	3.01	3.00	1.38	−0.47	1-Isopropyl-5-α-thienylhydantoin
2.90	2.72	3.19	3.03	1.28	−0.36	1-Allyl-5-α-thienylhydantoin
2.59	3.10	2.81	3.03	2.08	−0.39	1-*n*-Butyl-5-α-thienylhydantoin
3.04	3.10	3.36	3.34	0.34	1.24	5-Phenylhydantoin
4.44	4.15	3.95	3.76	2.47[f]	1.24	Diphenylhydantoin
2.75	2.95	2.99	3.03	0.03	1.24	5-α-Thienylhydantoin
3.82	3.84	3.84	3.95	1.84	1.24	5,5-Di-α-thienylhydantoin
3.92	3.99	3.83	3.89	2.15	1.24	5-Phenyl-5-α-thienylhydantoin

Acute Lethal Toxicity, —log 1/C, moles/kg. Obs.[u]	Calc.[v]	log P	Compound
2.55	2.51	0.14	*N*-Dimethylaminoethyl-γ-butyrolactam
2.59	2.57	0.32	*N*-Diethylaminoethyl-δ-valerolactam
2.61	2.70	0.74	*N*-Diethylaminoethyl-ε-caprolactam
3.10	3.11	2.06	*N*-(3-Diethylaminopropyl)-*o*-phenyleneurea
3.12	3.08	1.97	4-(2-Keto-1-benzimidazolinyl)-piperidine[w]

[a] From *Reference 14*. [b] Calculated from Eq. 3. [c] Calculated from Eq. 5. [d] Calculated from Eq. 7. [e] From *Reference 21*. [f] From C. Hansch, private communication. [g] Estimated value. [h] For the undissociated form. [i] From *Reference 8*. [j] From *Reference 22*. [k] Calculated from Eq. 9. [l] Calculated from Eq. 11. [m] From *Reference 23*. [n] From *Reference 24*. [o] Calculated from Eq. 12. [p] Calculated from Eq. 14. [q] Calculated from Eq. 16. [r] Calculated from Eq. 18. [s] Calculated from Eq. 20. [t] From this study. [u] Calculated from Eq. 23. [v] This compound, m.p. 185–187°, was purchased from Aldrich Chemical Co.

EXPERIMENTAL[1]

The mathematical model used in the regression analysis was first developed by Hansch *et al.* (1, 6), and used fairly extensively by our group as well as many other investigators (7–11). The equations correlating the biological activity with the physicochemical constants were derived *via* the method of least squares using a computer[2]. The biological data and the physicochemical constants used in the study are assembled in Table I. The log *P* values were calculated from the log *P* of the parent molecule and the π values of the substituent, unless otherwise stated. Octanol-water was the solvent system used in measuring *P*. The dipole moment values were either taken from the literature or estimated from the moment of the homolog.

Materials—The *N*-diethylaminoethyl lactams were synthesized by treating the corresponding lactam with equivalent amounts of sodium hydride and diethylaminoethyl chloride, using dioxane as the solvent (12), and were then purified on a cationic ion-exchange resin and alumina column.

N-Diethylaminoethyl-δ-valerolactam—Boiling point 148° (6.5 mm. Hg), yield 41%.

Anal.—Calc. for $C_{11}H_{22}N_2O$: C, 66.62; H, 11.18; N, 14.12. Found: C, 66.85; H, 11.05; N, 14.20.

[1] The elemental analyses were performed by C. F. Geiger of Ontario, Calif.

[2] IBM 360/65.

Table II—Equations Correlating CNS Activity with Physicochemical Constants

Animal	Test	Compounds	Number	Equation	n	r	s	log P_0 (±95% CL)
Mice	Antielectroshock	Cyclohexanones, *etc.*	1	$\log 1/C = -0.138 (\log P)^2 + 0.736 \log P + 2.323$	8	0.43	0.47	2.66 (± ∞)[a]
			2	$\log 1/C = -0.212 \mu + 3.588$	8	0.51	0.41	—
			3	$\log 1/C = -0.267 (\log P)^2 + 1.423 \log P - 0.368 \mu + 2.619$	8	0.89	0.26	2.66 (1.64–3.17)
Mice	Muscle relaxant	Cyclohexanones, *etc.*	4	$\log 1/C = -0.237 (\log P)^2 + 1.181 \log P + 1.591$	8	0.68	0.36	2.49 (± ∞)
			5	$\log 1/C = -0.313 (\log P)^2 + 1.601 \log P - 0.276 \mu + 1.895$	8	0.92	0.21	2.56 (2.08–2.85)
Mice	Acute lethal toxicity	Cyclohexanones, *etc.*	6	$\log 1/C = -0.138 (\log P)^2 + 0.729 \log P + 1.649$	8	0.42	0.38	2.65 (± ∞)
			7	$\log 1/C = -0.217 (\log P)^2 + 1.166 \log P - 0.286 \mu + 1.964$	8	0.85	0.25	2.69 (± ∞)
Mice	Antielectroshock	Miscellaneous	8	$\log 1/C = -0.222 (\log P)^2 + 1.153 \log P - 0.368 \mu + 2.994$	18	0.92	0.24	2.59 (2.39–2.84)
Mice	Antielectroshock	Hydantoins	9	$\log 1/C = 0.490 \log P + 0.525 E_s(R_1) + 2.286$	11	0.92	0.26	—
Rats	Antielectroshock	Hydantoins	10	$\log 1/C = 0.298 \log P + 0.373 E_s(R_1) + 2.727$	11	0.91	0.19	—
			11	$\log 1/C = -0.330 (\log P)^2 + 1.124 \log P + 0.540 E_s(R_1) + 2.330$	11	0.96	0.14	1.70 (1.45–3.88)
Mice	Antipentylenetetrazol-induced seizures	Barbiturates, hydantoins, imides	12	$\log 1/C = 1.023 \log P - 1.224$	5	0.98	0.21	—
			13	$\log 1/C = 0.998 \log P - 0.482 \mu - 0.486$	5	0.996	0.116	—
Mice	Antipentylenetetrazol-induced seizures	Barbiturates, hydantoins, imides	14	$\log 1/C = -0.142 (\log P)^2 + 0.695 \log P - 0.111$	13	0.93	0.22	2.44 (1.68–9.57)
			15	$\log 1/C = -0.145 (\log P)^2 + 0.716 \log P - 0.093$	10	0.94	0.24	2.47 (± ∞)
			16	$\log 1/C = -0.123 (\log P)^2 + 0.588 \log P - 0.597 \mu + 0.825$	10	0.99	0.12	2.39 (1.72–5.39)
Mice	Acute lethal toxicity	Barbiturates, hydantoins, imides	17	$\log 1/C = -0.207 (\log P)^2 + 0.802 \log P - 0.523$	15	0.84	0.37	1.94 (1.36–12.6)
			18	$\log 1/C = -0.210 (\log P)^2 + 0.856 \log P - 0.510$	14	0.94	0.23	2.04 (1.59–3.56)
			19	$\log 1/C = -0.236 (\log P)^2 + 0.877 \log P - 0.381$	10	0.98	0.16	1.83 (1.48–2.64)
			20	$\log 1/C = -0.226 (\log P)^2 + 0.800 \log P - 0.361 \mu + 0.175$	10	0.99	0.11	1.77 (1.49–2.26)
Mice	Acute lethal toxicity	Lactams, thiolactams, ureas, thioureas	21	$\log 1/C = -0.373 (\log P)^2 + 1.010 \log P + 0.227 \mu + 1.405$	22	0.83	0.31	1.35 (1.11–1.78)
			22	$\log 1/C = -0.364 (\log P)^2 + 1.005 \log P + 0.247 \mu + 1.298$	20	0.89	0.24	1.38 (1.17–1.71)
Mice	Acute lethal toxicity	*N*-Substituted lactams, *o*-phenyleneureas	23	$\log 1/C = 0.312 \log P + 2.468$	5	0.98	0.06	>2.0

[a] *CL* = confidence limits.

N-Diethylaminoethyl-ε-caprolactam—Boiling point 131–134° (6 mm. Hg), yield 34%.

Anal.—Calc. for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.62; H, 11.07; N, 12.97.

N-Diethylaminoethyl-γ-butyrolactam—Boiling point 120–124° (6.5 mm. Hg), yield 38%.

Anal.—Calc. for $C_{10}H_{20}N_2O$: C, 65.17; H, 10.93; N, 15.19. Found: C, 64.96; H, 10.78; N, 15.00.

Similar procedures were used to prepare the substituted *o*-phenyleneurea using *N*-dimethylformamide as the solvent.

N-(3-Dimethylaminopropyl)-o-phenyleneurea—Melting point 69–72°, yield 4%.

Anal.—Calc. for $C_{12}H_{17}N_3O$: C, 65.71; H, 7.82; N, 19.15. Found: C, 65.22; H, 7.67; N, 19.10.

The structures of these lactam and urea derivatives were confirmed by IR and NMR.

γ-Butyrolactone (n^{25}_D = 1.4354), α-methyl-γ-butyrolactone (n^{25}_D = 1.4318), γ-valerolactone (n^{25}_D = 1.4324), and δ-valerolactone (n^{25}_D = 1.4564) were purchased[3] and used without further purification. γ-Heptalactone was obtained from a commercial source[4] and used directly.

[3] Aldrich Chemical Co.
[4] K & K Laboratories.

CNS Activity and General Signs—Groups of six mice, three males and three females weighing 17–27 g., were injected intraperitoneally with the aqueous solution of the compound (0.3–1.2 ml.). Signs of CNS activity or other changes were observed continuously for 2 hr. and then at regular intervals for 2 days.

Preliminary Test for LD_{50}—The previously reported method (13) was used to determine the LD_{50} of the *N*-substituted lactams and the *o*-phenyleneurea derivative.

RESULTS AND DISCUSSION

The equations correlating the biological activity with the physicochemical parameters are summarized in Table II. The optimum lipophilic character (log P_0) for maximum CNS activity was obtained by setting (log $1/C$)/log P = 0. The log P_0 values with well-defined 95% confidence intervals are assembled in Table IV according to the descending order of log P_0.

Equations 1–7 were derived from three different tests of series of cyclohexanones and cyclohexyl benzyl alcohols reported by Brodie *et al.* (14). Equation 8 was obtained from these compounds plus imides, barbiturates, hydantoins, *etc.* One should note the negative dependence of the activity on the dipole moment (μ) in Eqs. 3, 5, 7, and 8 and the very narrow log P_0 values for maximum activity (2.56–2.66, Eqs. 3 and 5 of Table II, with well-defined 95% confidence

Table III—Preliminary Screening of Neuropharmacological Activities of Lactones in Mice

Compound	Dosage, mg./kg. i.p	Observation
γ-Butyrolactone	750	6/6[a] loss of righting reflex, ataxia in 2 min., eyes bulged, 1/6 died, average sleeping time 1.5 hr.
α-Methyl-γ-butyrolactone	1000	3/6 normal, 3/6 mild sedation in 5 min.
γ-Valerolactone	1000	4/6 with both hind legs stretched out, 6/6 mild sedation in 5 min.
	2000	2/2 moderate sedation, irregular respiration, hind legs paralyzed
δ-Valerolactone	750	6/6 mild sedation, 3/6 with bulging eyes
γ-Heptalactone	100	4/6 with sluggish hind-leg movement
	300	2/6 with sluggish hind-leg movement
	1000	3/6 with one hind leg paralyzed, 2/6 with both hind legs paralyzed, no apparent CNS activity
γ-Thiobutyrolactone	100	5/6 clonic and tonic convulsions[b]

[a] Ratio of number of animals responding to number of animals tested. [b] From *Reference 13*.

intervals). Equations 9–11 correlate the antielectroshock activity of 11 substituted hydantoins with log P and the Taft's steric constant E_s of the substituent at the N_1 position. The positive dependence on E_s indicates that a bulky substituent at the N_1 position will retard the anticonvulsant activity. This is in agreement with the well-known fact that alkylation of both nitrogens of a barbiturate tends to confer convulsant activity. The $(\log P)^2$ term was not justifiable in Eq. 9, where mice were the test animals. In rats (Eq. 11) the log P_0 value is very close to the previously reported value of 1.75 (8).

For anticonvulsant activity against pentylenetetrazol[4]-induced seizures, Eqs. 12–16 were obtained. Again there is negative dependence of activity on the dipole moment (Eqs. 13 and 16). The μ term in Eq. 13 is not significant at the 90 percentile level, since only five data points are available. The μ term in Eq. 16 is significant at the 97.5 percentile level, as indicated by an F test ($F_{1,6} = 13.8$, $F_{1,6_{0.975}} = 8.8$). Equations 17 and 18 were derived from the LD_{50} of series of barbiturates, hydantoins, amides, imides, *etc.* Since the log P_0 of 2.04 is only slightly below the log P_0 of 2.4–2.6 for antielectroshock or hypnotic activity, one should not expect complete separation of the acute lethal toxicity from the therapeutic effect by merely changing the lipophilic character of these drugs.

Equations 19 and 20 correlate the acute lethal toxicity of 10 CNS depressants among barbiturates, hydantoins, and imides. Equation 21 was obtained from the acute lethal toxicity data of 22 CNS stimulants belonging to different chemical groups and reported in two separate papers previously (9, 10). The dependence of the dipole moment (μ) is positive in contrast with that of CNS depressants or anticonvulsants. The correlation coefficient (r) increased from 0.83 to 0.89 when two poorly predicted compounds were deleted (Eq. 22). The μ term is significant at the 95 percentile level in Eq. 21, and it is significant at the 99.5 percentile level in Eq. 22. The log P_0 for the acute lethal toxicity of these convulsants is about 1.4.

Equation 23 was derived from the LD_{50} of N-substituted lactams and o-phenyleneureas, studied for the first time in these laboratories. Since the highest log P value of these five compounds was 2.06, a linear rather than a parabolic equation of log P was obtained.

Results of the preliminary screening for the CNS activity and other neuropharmacological activities of lactones are shown in Table III. From Table III, it is evident that the CNS depressant activity of γ-butyrolactone is decreased rather than increased when a methyl group is attached to the α- or γ-position. No loss of righting reflex was observed for these lactones at the 1000-mg./kg. level. The six-membered δ-valerolactone also showed lower CNS depressant activity as compared with γ-butyrolactone. For the most lipophilic, γ-heptalactone, no CNS activity was apparent even at the 1000-mg./kg. level; however, partial paralysis of the hind legs was observed even at 100-mg./kg. level, indicating local anesthetic activity on the peripheral nervous system. A similar phenomenon was observed for γ-valerolactone (1000 mg./kg.). Bulging eyes were observed for the lactones without a side chain (γ-butyrolactone and δ-valerolactone). Many lactones are known to have depression action on earthworms, frog gastrocnemius, rabbit small intestine, and frog heart (15).

It is known that γ-hydroxybutyric acid, when administered to animals or man, is converted to γ-butyrolactone and causes sleep. It was also reported (3) that the induced sleep in rats is related to the concentration of the lactone in the brain when the acid or the lactone is administered. Giarman and Schmidt (2) demonstrated that γ-butyrolactone alters the levels of endogenous acetylcholine in the brains of mice and rats. Concentration of acetylcholine in the cerebral cortex is increased by γ-butyrolactone, with a time course parallel to the degree of depression of the animal.

The results of this structure–activity analysis reflect the steric and hydrophilic aspects of the binding site for acetylcholine and γ-butyrolactone. An additional alkyl group at the α- or γ-position decreases the CNS activity even though the lipophilic character is increased. Since an alkyl group on the lactone ring decreases the activity and the most lipophilic member (γ-heptalactone) does not give any apparent CNS activity at 1000 mg./kg., the binding site of acetylcholine conceivably may be surrounded by a hydrophilic rather than a lipophilic region. It is well established that the active site of acetylcholinesterase is composed of imidazole nitrogen, a serine hydroxy group, and an anionic site (16). A similar decrease in acute toxicity was reported (5) for a series of γ-methyl-α-alkyl butyrolactones as the α-alkyl group is lengthened from C_2 to C_6.

On the other hand, Roth and Suhr (17) reported that γ-butyrolactone increases brain dopamine by blocking the release of this amine from dopamine-containing neurons. It is also suggested that the CNS depressant properties of γ-hydroxybutyrate may be related to this block in the release of brain dopamine.

While γ-butyrolactone is a CNS depressant, its sulfur analog γ-thiobutyrolactone has been shown to be a convulsant (13). Ito (18) also reported that running fits are induced in mice by intraperitoneal injection of 150–200 mg./kg. of γ-mercaptobutyric acid after a latent period of 4–8 min. It is quite possible that γ-mercaptobutyric acid also cyclizes *in vivo* to produce the fairly potent CNS stimulant γ-thiobutyrolactone. It is not clear at present why the CNS activity is changed from a depressant to a stimulant by replacing —COO— with —COS—. It also remains to be clarified whether γ-thiobutyrolactone acts at the same site as γ-butyrolactone *via* the same mechanism.

It was reported (19) that lactones are not hydrolyzed by esterases that attack the ordinary open-chain esters. Butyrolactone, γ-valerolactone, *etc.*, in alkaline medium showed no appreciable hydrolysis by liver esterase preparations that were reactive toward methyl butyrate. On the contrary, lactones inhibited the cleavage of the ester, presumably due to the formation of a stable complex with the enzyme (19). These findings suggest that lactones and γ-thiobutyrolactones are probably the pharmacologically active species rather than the hydrolyzed products.

Table IV summarizes the ideal lipophilic character (log P_0) for maximum CNS activity under various testing conditions. As reported (1, 20) previously, the log P_0 for many centrally acting drugs centered around 2.0 ± 0.7, with two distinct exceptions at the end of Table IV. γ-Butyrolactone appeared to be the most potent CNS depressant among the several lactone derivatives examined.

γ-Butyrolactone should have a log P less than 0.71, the calculated log P value of the open-chain methyl propionate. In the case of 2-sulfamoylbenzoates, the most potent member has a log P of -0.13 and the dependence on log P is negative, therefore, a log P_0 of < -0.13 is expected for this series of compounds.

The relatively narrow range of log P_0 (2.0 ± 0.7) for the many compounds containing a polar amido, thioamido, keto, or alcoholic group strongly suggests that the rate-limiting step for the CNS action caused by these compounds is probably the same, namely the penetration of the tightly packed neuroglial cells by these compounds.

[4] Metrazole.

Table IV—Optimum Lipophilic Character (log P_0) for Maximum CNS Activity

Animal	Compounds	Number of Data Points	CNS Activity	log P_0 (±95% CL)	Reference
Mice	Cyclohexanones, *etc.*	8	Antielectroshock	2.66 (1.64–3.17)	14
Mice	Barbiturates, hydantoins, imides, cyclohexanones, *etc.*	18	Antielectroshock	2.59 (2.39–2.84)	This study, 8, 14
Mice	Cyclohexanones, *etc.*	8	Muscle relaxant	2.56 (2.08–2.85)	14
Mice	Barbiturates	10	Hypnotic	2.40	1
Mice	Barbiturates, hydantoins, imides	10	Antipentylenetetrazole-induced seizures	2.39 (1.72–5.39)	24
Mice	Barbiturates, hydantoins, imides	14	Acute lethal toxicity (CNS depression)	2.04 (1.59–3.56)	24
Mice	Barbiturates, hydantoins, imides	10	Acute lethal toxicity (CNS depression)	1.77 (1.49–2.26)	24
Rats	Hydantoins	11	Antielectroshock	1.70 (1.45–3.88)	22
Mice	Ureas, thioureas, lactams, thiolactams	20	Acute lethal toxicity (CNS stimulation)	1.38 (1.17–1.71)	This study, 7, 10
Mice	γ-Butyrolactones	5	CNS depression	<0.71	This study
Mice	2-Sulfamoylbenzoates	9, 12	Antistrychnine Antielectroshock	<0.13	11

The finding of the dependence on the dipole moment also suggests that in the development of new anticonvulsants or sedative–hypnotics of comparable structures, it would be highly desirable to have a minimum resultant dipole moment on the polar moiety, while for a potent CNS stimulant or analeptic agent, high dipole moment enhances the activity.

Entirely different sites and mechanisms of action appear to be evident from the very low log P values of γ-butyrolactone and series of 2-sulfamoylbenzoates.

REFERENCES

(1) C. Hansch, A. R. Steward, J. Iwasa, and E. W. Deutsch, *Mol. Pharmacol.*, **1**, 205(1965).

(2) N. J. Giarman and K. F. Schmidt, *Brit. J. Pharmacol.*, **20**, 563(1963).

(3) S. P. Bessman and S. J. Skolnik, *Science*, **143**, 1045(1964).

(4) H. Hampel and H. J. Hapke, *Arch. Int. Pharmacodyn. Ther.*, **171**, 306(1968).

(5) W. Prastowski, *Arch. Immunol. Ther. Exp.*, **16**, 827(1968).

(6) C. Hansch, A. R. Steward, S. M. Anderson, and D. Bentley, *J. Med. Chem.*, **11**, 1(1968).

(7) E. J. Lien, M. Hussain, and M. P. Golden, *ibid.*, **13**, 623 (1970).

(8) E. J. Lien, *ibid.*, **13**, 1189(1970).

(9) M. H. Hussain and E. J. Lien, *ibid.*, **14**, 138(1971).

(10) E. J. Lien, L. L. Lien, and G. L. Tong, *ibid.*, **14**, 846(1971).

(11) G. Hamor and E. J. Lien, *Farmaco, Ed. Sci.*, **24**, 704(1969).

(12) E. J. Lien and W. D. Kumler, *J. Med. Chem.*, **11**, 214(1968).

(13) C. Elison, E. J. Lien, A. P. Zinger, M. Hussain, G. L. Tong, and M. Golden, *J. Pharm. Sci.*, **60**, 1058(1971).

(14) D. C. Brodie, A. C. Huitric, and W. D. Kumler, *J. Amer. Pharm. Ass., Sci. Ed.*, **47**, 240(1958).

(15) W. F. von Oettingen, *J. Pharmacol.*, **36**, 335(1929).

(16) R. M. Krupka and K. J. Laidler, *J. Amer. Chem. Soc.*, **83**, 1458(1961).

(17) R. H. Roth and Y. Suhr, *Biochem. Pharmacol.*, **19**, 3001 (1970).

(18) N. Ito, *ibid.*, **18**, 2605(1969).

(19) E. Bamann and M. Schmeller, *Z. Physiol. Chem.*, **194**, 14 (1931).

(20) C. Hansch and S. M. Anderson, *J. Med. Chem.*, **10**, 745 (1967).

(21) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963.

(22) C. R. Ensor and G. Chen, *Arch. Neurol. Psychiat.*, **62**, 857 (1949).

(23) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p. 228.

(24) J. G. Millichap, in "Physiological Pharmacology," vol. II, W. S. Root and F. G. Hofmann, Eds., Academic, New York, N. Y., 1963, p. 137.

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