both isomers cyclization causes deformation of this ring to a half-chair.

It is also of interest to note that since cyclized *cis*- and *trans*-HPIPA differ in configuration only at the phosphorus atom, interconversion could be mediated through the same mechanisms as proposed for uncyclized *cis*- and *trans*-HPIPA.[7]

D. Relationship of Conformation to Biological Activity. In forming the bicyclic peroxide from HPIPA, the chloroethyl group attached to N3 is inactivated by intramolecular reaction with the C4 hydroperoxide, leaving the cyclized HPIPA's with only one alkylating moiety. Thus, these compounds are not attractive as prospective antineoplastic agents, and their biological activity has not been investigated. Nevertheless, crystal structure determinations of the two cyclized HPIPA epimers has provided data highly relevant to structure–activity relationships in the cyclophosphamide family of anticancer drugs.

As stated earlier, all the C4-hydroxylated, preactivated, cyclophosphamide derivatives characterized to data have the C4-oxygen substituent in the axial position, regardless of whether hydroxylation has been achieved by ozonolysis of open-chain compounds[2,6] or by the Fenton oxidation of cyclophosphamide.[5] Since all of the synthetically prepared compounds are essentially equivalent in biological activity, it seemed reasonable to suggest[8] that this arrangement is the most stable one and is likely the configuration of the 4-hydroxy derivatives produced in the in vivo activation of cyclophosphamide and its analogues.

The validity of these conclusions was questioned, however, by the cyclized HPIPA NMR spectra, which were interpreted as showing the C4 oxygen in the equatorial position in the trans epimer. The change in conformation at C4 (and at phosphorus) in going from *trans*-HPIPA to cyclized *trans*-HPIPA was rationalized by postulating the C4-oxygen axial conformation to be an unstable intermediate.[6] If a change in the environment of the C4-oxygen atoms, such as in the formation of the bicyclic peroxide, can render the C4-oxygen axial geometry unstable and cause an inversion to the equatorial oxygen configuration, it is conceivable that similar forces could operate in the enzymatic hydroxylation process or during the cellular uptake of the hydroxylated derivatives. Crystal structure determinations of the cyclized HPIPA's demonstrate, however, that the C4-oxygen axial configuration is a stable arrangement for both epimers in the solid state and, furthermore, provide a stereochemical basis for reinterpretation of the cyclized *trans*-HPIPA NMR spectrum to suggest that this configuration is the stable one in solution also. Thus, these crystal structure results are consistent with and strongly reinforce the structure–activity correlations previously postulated for the cyclophosphamide family of drugs.

Acknowledgment. We thank Dr. A. Takamizawa for supplying samples of the title compounds and Drs. A. Grey and N. Andersen for helpful discussions of the NMR spectra. Support was from the Medical Research Council of Canada and from the National Cancer Institute, United States Public Health Service (Grant CA 15879).

Registry No. cyclized *cis*-HPIPA, 64858-46-4; cyclized *trans*-HPIPA, 64858-45-3.

Supplementary Material Available: Atomic coordinates, thermal parameters, and observed and calculated structure factors for both structures (17 pages). Ordering information is given on any current masthead page.

Quantitative Structure–Activity Relationship of Double Alkyl Chain Drugs

Sakae Hada, Saburo Neya, and Noriaki Funasaki*

Kyoto College of Pharmacy, Yamashina-ku, Kyoto 607, Japan. *Received August 16, 1982*

The quantitative structure–activity relationship of double alkyl chain drugs, including alkanols, aliphatic esters, ketones, barbiturates, amphetamines, butyrylcholinesterase inhibitors, antimalarials, and rifamycin amides, is investigated. A series of double-chain homologues, $C_nH_{2n+1}XC_mH_{2m+1}$, in which n changes, keeping m constant, is classified into three types: in type IIL, $n > m$; in type IIE, $n = m$; in type IIS, $n < m$. When a linear relationship, vis., $\log (1/C) = an + b$, holds, the slope a depends on the type; $a_I \geq a_{IIL} > a_{IIE} > a_{IIS}$. Here a_I means the slope for single-chain homologues. The same order is observed for the equation, log hydrophobicity = $an + b$, where the hydrophobicity of drug denotes the water solubility, the critical micelle concentration, and the partition coefficient for the 1-octanol–water phases. Therefore, decreased biological activity of a double-chain drug relative to that of a single-chain isomer can be explained by a decreased hydrophobicity of the double-chain drug, due to the intramolecular association of these chains in water. When a parabolic relationship between log $(1/C)$ and n holds, the optimum n depends on the type: $n_{opI} < n_{opIIL} < n_{opIIE}$. This order is also explicable on the basis of a decreased hydrophobicity of double-chain drug. The N-dealklation rate of amphetamines in vivo appears to be affected by the steric factor as well as the hydrophobic factor. A decreased hydrophobicity of double-chain compounds should be taken into consideration for estimating their partition coefficients.

Hydrophobic substances or groups play an important role in forming the high-order structure of biomembranes, proteins, micelles, liposomes, etc. in aqueous media.[1] We have shown that such a hydrophobic effect exists in low-molecular-weight compounds; e.g., two or three alkyl chains of sulfoxides,[2] ethyleneglycol diesters,[3] and triglycerides[4] aggregate intramolecularly in aqueous solutions. The logarithms of the critical micelle concentration (cmc) of dialkyl sulfoxides and of the solubility (C_s) of ethylene glycol diesters and triglycerides in water are correlated linearly with the total number of carbon atoms (n) in these molecules according to eq 1, and the coefficients (a) for

$$\log (\text{cmc or } C_s) = -an + b \quad (1)$$

these double- and triple-chain compounds are smaller than that for single-chain compounds.[2-4] A similar effect may

(1) C. Tanford, "The Hydrophobic Effect: Formation of Micelles and Biological Membranes", Wiley-Interscience, New York, 1973.
(2) N. Funasaki and S. Hada, *J. Colloid Interface Sci.*, 64, 454 (1978).
(3) N. Funasaki, S. Hada, and K. Kawamura, *Nippon Kagaku Kaishi*, 1944 (1976).
(4) N. Funasaki, S. Hada, and K. Suzuki, *Chem. Pharm. Bull.*, 24, 731 (1976).

0022-2623/83/1826-0686$01.50/0

be observed for the biological activities of double-chain drugs.

In recent years, considerable effort and study have been made in attempting to correlate the relative biological response to drugs with their molecular structures. Among the most successful and widely known approaches has been the use of linear free energy by Hansch and co-workers to develop structure–activity relationships.[5-7] According to Hansch et al.,[5-9] a structure–activity relationship can be generally written as eq 2, where C is the molar concentration of drug producing a standard response, σ is the Hammett substituent constant, E_s is the steric factor, and A, B, and ρ are constants. A notable observation in their work is that there appear to be more or less constant additive terms to the partition coefficients (P) for a variety of groups on a parent molecule.

$$\log (1/C) = A \log P - B(\log P)^2 + \rho\sigma + \delta E_s + \text{constant} \quad (2)$$

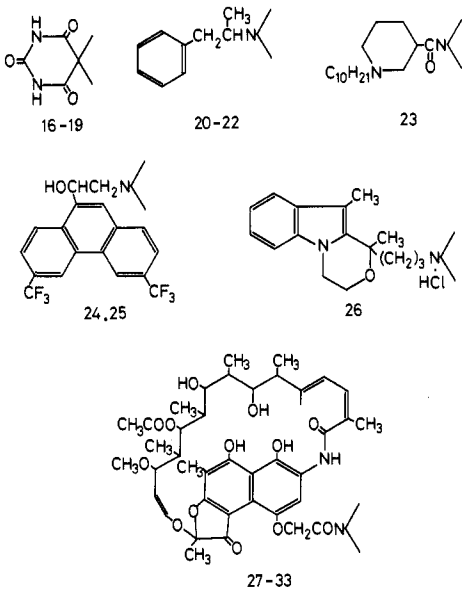
In this work, we deal with the structure–activity relationship of double-chain drugs in terms of the Hansch equation. Double-chain drugs have smaller P values than the single-chain isomer because of the intramolecular association of the two alkyl chains in water. This correction for the P values of double-chain drugs leads to a better structure–activity relationship of double-chain drugs.

Results

Classification of Drugs by the Number of Alkyl Chains. Chemical compounds possessing two alkyl chains on a molecule can be generally written as $C_nH_{2n+1}XC_mH_{2m+1}$, where X can be either an atom or a group. These compounds are classified as type II, which refers to compounds possessing two alkyl chains on a molecule. We are interested in a series of double-chain compounds in which one alkyl chain (m) is kept unchanged and in which the other (n) is elongated. We classified a series of double-chain compounds of $m > n$ as type IIS, those of $m < n$ as type IIL, and those of $m = n$ as type IIE.

Double-chain drugs whose biological activities have been reported are collected in Table I. 1-Alkanols belong to type I. 2-Alkanols are classified into type IIL. Alkanols possessing a hydroxy group in the middle of a chain are classified into type IIE. In Table I, three types of barbiturates are included. One of the two alkyl chains is commonly the ethyl group, but the other chain is dependent on the type. Type IIL_1 has an alkyl chain longer than the ethyl group. Each of the types IIL_2 and IIE has a branched alkyl chain. General formulas of the branched chains of type IIL_2 and IIE are $-CH(CH_3)C_n$ and $-CH(C_{0.5n})_2$, respectively.

Chart I



A butyrylcholinesterase inhibitor (**23** in Table I) has a decyl group, but this group cannot associate with another chain(s), substituted on the nitrogen atom of the amide group, since these alkyl chains are separated by five atoms on a parent molecule. Butyrylcholinesterase inhibitors, therefore, are classified not as types II and III (triple chain) but as types I and II. As this example shows, all molecules described in Table I are classified on the basis of the number of intramolecularly associable alkyl chains instead of the total number of alkyl chains. The intramolecular association of two alkyl chains is expected to depend on the distance between these chains, the bond angle, the length of alkyl chains, the solvent, etc. The chemical structure of compounds concerned with the present study is given in Chart I.

Linear Relationships. When the chain length of a series of compounds (homologues) changes, keeping the

(5) C. Hansch and W. J. Dunn III, *J. Pharm. Sci.*, **61**, 1 (1972).
(6) C. Hansch and J. M. Clayton, *J. Pharm. Sci.*, **62**, 1 (1973).
(7) S. S. Davis, T. Higuchi, and J. H. Rytting, *Adv. Pharm. Sci.*, **4**, 73 (1974).
(8) C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Am. Chem. Soc.*, **85**, 2817 (1963).
(9) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
(10) D. J. Crisp and D. H. A. Marr, *Proc. Int. Congr. Surf. Act., 2nd*, 310 (1957).
(11) H. C. Brill and A. K. Presnell, *Ohio J. Sci.*, **41**, 431 (1941).
(12) W. P. Read, *Annu. Appl. Biol.*, **35**, 432 (1948).
(13) D. Glick and C. G. King, *J. Biol. Chem.*, **94**, 497 (1932).
(14) T. T. Herskovits, B. Gadegbeku, and H. Jaillet, *J. Biol. Chem.*, **245**, 2588 (1970).
(15) H. M. Vernon, *J. Physiol.*, **43**, 325 (1911).
(16) R. H. Baechler, *Proc. Annu. Meet. Am. Wood-Preserv. Assoc.*, **43**, 94 (1947).
(17) N. Sapeika, *Arch. Int. Pharmacodyn. Ther.*, **50**, 296 (1935).
(18) I. A. Kamil, J. N. Smith, and R. T. Williams, *Biochem. J.*, **53**, 129 (1953).
(19) H. M. Vernon, *Biochem. Z.*, **47**, 374 (1912).
(20) J. Ferguson and H. Pirie, *Annu. Appl. Biol.*, **35**, 532 (1948).
(21) H. Führer and E. Neubauer, *Naunyn-Schmiederberg's Arch. Exp. Pathol. Pharmakol.*, **56**, 333 (1907).
(22) C. Hansch and W. R. Glave, *Mol. Pharmacol.*, **7**, 337 (1971).
(23) H. A. Shonle and A. Moment, *J. Am. Chem. Soc.*, **45**, 243 (1923).
(24) C. Hansch, A. R. Steward, S. M. Anderson, and D. Bentley, *J. Med. Chem.*, 11, 1 (1968).
(25) G. H. A. Glowes, A. K. Keltch, and M. E. Krahl, *J. Pharmacol. Exp. Ther.*, **68**, 312 (1940).
(26) C. Hansch and S. M. Anderson, *J. Med. Chem.*, **10**, 745 (1967).
(27) F. A. Fuhrmann and J. Field, *J. Pharmacol. Exp. Ther.*, **77**, 392 (1943).
(28) A. J. Stuper and P. C. Jurs, *J. Pharm. Sci.*, **67**, 745 (1978).
(29) B. Testa and B. Salvesen, *J. Pharm. Sci.*, **69**, 497 (1980).
(30) M. Donike, R. Iffland, and L. Jaenicke, *Arzneim.-Forsch.*, **24**, 556 (1974).
(31) J. M. Clayton and W. P. Purcell, *J. Med. Chem.*, **12**, 1087 (1969).
(32) C. Hansch and J. Fukunaga, *CHEMTECH*, **7**, 120 (1977).
(33) C. A. Demerson, G. Santroch, L. G. Humber, and M. P. Charest, *J. Med. Chem.*, 18, 577 (1975).
(34) P. Sensi, N. Maggi, R. Ballotta, S. Fürész, R. Pallanza, and V. Arioli, *J. Med. Chem.*, **7**, 596 (1964).
(35) F. R. Quinn, J. S. Driscoll, and C. Hansch, *J. Med. Chem.*, 18, 332 (1975).

Table I. Parameters of Structure–Activity Relationship

no.	compd	type (n)	a	a/a_I	n_{op}	A	log P_{op}	biol act.[a]	ref[b]
				Alcohol					
1	I; C_nOH	I (1–8)	0.55 ± 0.07	1.00		1.02 ± 0.07		C; narcosis, larvae	10, 5
	IIL;	IIL (3, 4)	0.240	0.44		0.511		barnacle	
2	$C_{n-2}CH_3CHOH$	I (1–4)	0.63 ± 0.07	1.00		1.29 ± 0.14		C; narcosis, goldfish	11, 5
	IIE;	IIL (3, 4)	0.400	0.63		0.830			
3	$(C_{0.5n-0.5})_2CHOH$	I (1–5)	0.363 ± 0.005	1.00		0.70 ± 0.01		C; toxicity of vapor,	12, 5
	IIS;	IIL (3–5)	0.303 ± 0.005	0.83		0.59 ± 0.01		tomato plant	
	$C_{n-3}(C_2)CHOH$	IIE (3, 5)	0.255	0.70		0.500			
		IIS (4,5)	0.230	0.63		0.418			
4		I (1–5)	0.35 ± 0.03	1.00		0.72 ± 0.02		C; toxicity of vapor,	12, 5
		IIL (3–5)	0.30 ± 0.02	0.86		0.57 ± 0.06		red spider	
		IIE (3, 5)	0.275	0.79		0.539			
		IIS (4, 5)	0.190	0.54		0.345			
5		I (1–9)	0.38 ± 0.02	1.00		0.76 ± 0.04		C; I_{25}, esterase,	13, 5
		IIL (4, 5)	0.610	1.60		1.110		liver, sheep	
6		I (1–4)	0.35 ± 0.03	1.00		0.70 ± 0.06		C; denaturation,	14, 5
		IIL (3, 4)	0.380	1.09		0.810		α-chymotrypsinogen	
7		I (1–4)	0.61 ± 0.06	1.00		1.15 ± 0.09		C; I_{50}, tortoise,	15, 5
		IIL (3, 4)	0.580	0.95		1.234		heart	
8		I (1–10)	0.50 ± 0.03	1.00		0.91 ± 0.05		C; MTD, Madison 517	16, 5
		IIL (3–5)	0.46 ± 0.01	0.93		0.84 ± 0.01		fungus	
		IIE (3, 5)	0.385	0.77		0.755			
		IIS (4, 5)	0.410	0.82		0.745			
9		I (1, 2, 5, 6)	0.38 ± 0.02	1.00		0.71 ± 0.10		C; MLD, South	17, 5
		IIL (3, 4)	0.310	0.81		0.660		African toad	
10		IIL (3–8)			6.5		2.0	RBR, rabit	18, 6
		IIE (3, 5, 7)			>7		>2.2	excretion	
				Ketone					
11	IIL; $C_{n-1}CH_3CO$	IIL (2–4)	0.48 ± 0.02			0.96 ± 0.04		C; I_{50}, indophenol	19, 5
	IIE; $(C_{0.5n})_2CO$	IIE (2, 4)	0.475			0.922		oxidation	
	IIS; $C_{n-2}(C_2)CO$	IIS (3, 4)	0.540			1.080			
12		IIL (2–4)	0.52 ± 0.07			1.00 ± 0.08		C; narcosis, larvae	10, 5
		IIE (2, 4)	0.515			1.000		barnacle	
		IIS (3, 4)	0.440			0.880			
13		IIL (2–4)	0.38 ± 0.06			0.68 ± 0.04		C; LD_{50}, grain,	20, 5
		IIE (2, 4)	0.340			0.660		weevil, vapor	
		IIS (3, 4)	0.250			0.500			
				Ester					
14	$HCOOC_n$	I (1–3)	0.47 ± 0.02	1.00		0.94 ± 0.10		C; HC, bovine	21, 22
	CH_3COOC_n	IIL (1–4)	0.47 ± 0.02	1.00		0.94 ± 0.10		erythrocyte	
	C_2COOC_n	IIL (2, 3)	0.450	0.96		0.900			
	$C_{0.5n}COOC_{0.5n}$	IIE (2, 4)	0.415	0.88		0.830			
	C_3COOC_n	IIS (1, 2)	0.370	0.79		0.740			
15	CH_3COOC_n	IIL (1–6)	0.450 ± 0.003			0.900 ± 0.006		C; MTD, Madison	16, 5
	C_3COOC_n	IIS (2, 3)	0.407			0.813		517 fungus	
	C_nCOOC_2	IIL (2–5)	0.463 ± 0.007			0.93 ± 0.01			
	C_nCOOC_5	IIS (1, 3)	0.350			0.700			

				Barbiturate				
16	IIL_1; $=C(C_2)C_n$	IIL_1 (2, 4)	0.315		0.630		C; MED, rabbit	23, 24
		IIL_2 (3, 4)	0.330		0.660			
17	IIL_2; $=C(C_2)CH(CH_3)C_{n-2}$	IIL_1 (2, 4-6)	0.44 ± 0.02		0.89 ± 0.04		C; I_{50}, arbica egg gels, pH 8	25, 26
		IIL_2 (3, 5)	0.565		1.130			
	IIE; $=C(C_2)CH(C_{0.5n-0.5})_2$	IIE (3, 5)	0.530		1.050			
18		IIL_1 (2, 4)	0.700		1.480		C; I_{50}, rat brain O_2 consumption	27, 6
		IIL_2 (3, 5)	0.590		1.180			
19		IIL_1 (2-7)		6		2.65	C; duration (min) of depressant effect	28, 6, 24, 26
		IIL_2 (3-5, 8)		7		3.0		
		IIE (3, 5, 7)		>7		>3.0		
				Amphetamine				
20	I; $-NHC_n$	I (1-4)		1		−1.5	RBR (PEU), % of excreted, unchanged, pH 5.0-5.2	29, 30
	IIL; $-N(CH_3)C_{n-1}$	IIL (2-5)		2		−0.3		
	IIE; $-N(C_{0.5n})_2$	IIE (2, 4, 6, 8)		3.5		0.3		
21		I (1-4)		1		−1.5	RBR (EXC), pH 5.0-5.2	29, 30
		IIL (2-5)		1.5		−1.0		
		IIE (2, 4, 6)		3		0.2		
22		I (1-4)	0.24 ± 0.03	1.00	0.34 ± 0.05		RBR (DEA), pH 5.0-5.2	29, 30
		IIE (2, 4, 6)	0.21 ± 0.02	0.88	0.28 ± 0.04			
				Butyrylcholinesterase Inhibitor				
23	$-CONHC_n$	I (1, 2)	0.400	1.00			C; I_{50}	31
	$-CON(C_{0.5n})_2$	IIE (2, 4, 6)	0.33 ± 0.02	0.83				
				Antimalarial				
24	$-NHC_n$	I (1-4, 6)		3		3.3	C; ED_{50}	32, 32
	$-N(C_{0.5n})_2$	IIE (6, 8)		>8		>5.7		
25	$-NHCH_2C_n$	I (0-3, 5)		2		3.3	C; ED_{50}	32, 32
	$-NHCH(C_{0.5n})_2$	IIE (2, 4, 6)		>6		>5.3		
				Antidepressant				
26	$-NHC_n$	I (1, 2)	0.160	1.00			C; LD_{50}	33
	$-N(C_{0.5n})_2$	IIE (2, 4)	0.115	0.72				
				Rifamycin B Amide				
27	I; $-NHC_n$	I (1-3)		2		0.32	C; MIC, *M. aureus*	34, 35
	IIL_1; $-N(CH_3)C_{n-1}$	IIL_1 (2-5)		>5		>1.82		
	IIL_2;	IIL_2 (4-6)		>6		>2.32		
		IIE (2, 4, 6, 8, 10)		>10		>4.32		
28	$-N(C_2)C_{n-2}$	I (1-3)		2		0.32	C; MIC, *S. faecalis*	34, 35
	IIE; $-N(C_{0.5n})_2$	IIL_1 (2-5)		4		1.32		
		IIL_2 (4-6)		>6		>2.32		
		IIE (2, 4, 6, 8, 10)		>10		>4.32		
29		I (1-3)		2		0.32	C; MIC, *S. hemolyticus*	34, 35
		IIL_1 (2-5)		>5		>1.82		
		IIL_2 (4-6)		5		1.82		
		IIE (2, 4, 6, 8, 10)		6		2.32		
30		I (1-3)		1		−0.18	C; MIC, *B. subtilis*	34, 35
		IIL_1 (2-5)		4		1.32		
		IIL_2 (4-6)		>6		>2.32		
		IIE (2, 4, 6, 8, 10)		>10		>4.32		
31		IIL_1 (2-5)	0.15 ± 0.02		0.30 ± 0.04		C; LD_{50}, mice, iv	34, 35
		IIL_2 (4-6)	0.15 ± 0.02		0.30 ± 0.04			
		IIE (2, 4, 6, 8)	0.12 ± 0.02		0.24 ± 0.04			

Table I (*Continued*)

no.	compound	type (n)	a	a/a_1	n_{op}	A	$\log P_{op}$	biol act.[a]	ref[b]
32		IIL_2 (4–6)	−0.11 ± 0.03			−0.22 ± 0.06		C; LD_{50}, mice, po	34, 35
		IIE (4, 6, 8)	−0.05 ± 0.01			−0.10 ± 0.02			
33		IIL_2 (4–6)	−0.22 ± 0.01			−0.44 ± 0.02		C; ED_{50}, mice, sc	34, 35
		IIE (4, 6, 8)	−0.16 ± 0.01			−0.32 ± 0.02			

[a] Abbreviations for biological systems and activities include: DEA = rate constant of the first N-dealkylation step (h^{-1}); ED_{50} = effective dose for 50% of the population; EXC = rate constant of urinary excretion (h^{-1}); HC = hemolysis concentration; $I_{50(25)}$ = concentration for 50% (25%) inhibition of the population, LD_{50} = lethal dose for 50% of the population, MED = minimum effective dose; MIC = minimum inhibitory concentration; MLD = minimum lethal dose; MTD = minimum toxic dose; PEU = percent of amphetamine derivatives excreted unchanged; RBR = relative biological response rather than log (1/C). [b] Biological activity data are taken from the first reference in this column, and partition coefficient data are from the remainder.

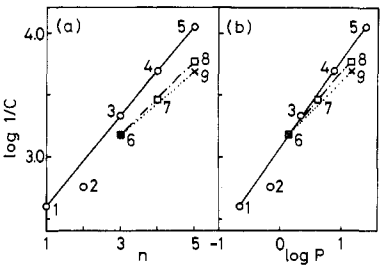


Figure 1. The toxicity of vapors of alcohols to tomato plants (3, Table I) as functions of the number of carbon atoms (a), and the logarithm of partition coefficients between 1-octanol and water (b). Nine alkanols are classified into types I (solid line), IIL (dot–dash line), and IIE (dotted line): 1, CH_3OH: 2, CH_3CH_2OH: 3, $CH_3(CH_2)_2OH$: 4, $CH_3(CH_2)_3OH$: 5, $CH_3(CH_2)_4OH$: 6, $(CH_3)_2CHOH$: 7, $CH_3CH_2CH(CH_3)OH$: 8, $CH_3(CH_2)_2CH(CH_3)OH$: 9, $(CH_3CH_2)_2CHOH$. The partition coefficients of alkanols 1, 3–5, and 7 are observed values, and those of the other alkanols are estimated from the "additivity" of partition coefficients.

parent group X constant, only the partition coefficient terms may change in eq 2. Therefore, we can rewrite eq 2 as eq 3. In most studies in the literature, workers have

$$\log (1/C) = A \log P - B(\log P)^2 + \text{constant} \quad (3)$$

been concerned with the effects of lower chain length homologues and have therefore followed drug action in the initial linear region of the parabolic drug action–lipophilicity equation, viz., eq 3. In addition, when the drug affects biomembranes or proteins nonspecifically under equilibrium conditions, one finds and expects linear relationships between log (1/C) and log P or n.[5-9]

$$\log (1/C) = an + \text{constant} \quad (4)$$

$$\log (1/C) = A \log P + \text{constant} \quad (5)$$

In Figure 1, such examples are shown for alcohols. As this figure shows, the coefficients a and A depend on the type classified herein. As Table I shows, these coefficients also depend on the kind of biological activity investigated. In Table I, the partition coefficients of a few parent molecules were experimentally determined, and others were estimated by assuming the additivity of the group free energy of transfer. All P values of the amphetamines shown in Table I are measured values for the heptane–water phases. Values of P for all drugs, except amphetamines, are for the 1-octanol–water phases, since very extensive studies correlating drug structure with biological response have been based on partition studies with 1-octanol.[5-9]

According to Hansch, the A values of drug homologues acting on biological membranes and on proteins are generally 1.07 ± 0.14 and 0.74 ± 0.09, respectively.[36] The coefficients a and A will vary depending on the various processes that the drug experiences until a biological response is exhibited after administration, e.g., membrane permeation, protein binding, membrane partition, metabolism, excretion, etc. Furthermore, these coefficients are expected to depend on the method of administration of the drug, the species of living body, whole body or tissue investigated, etc. Such factors are briefly referred to in the biological activity column of Table I. Direct comparisons between values of a and A, therefore, are not very significant for different biological activities and should be confined to different types of homologues.

(36) C. Hansch, *Adv. Chem. Ser.*, no. 114, 20 (1972).

Table II. Negative Slopes of Log C_s vs. n Plots for Double-Chain Compounds

compd	type	a (investigated n)	a/a_I
		Alcohol	
C_nOH	I	0.60 (4-9),[a] 0.718[b]	1.00
$C_n(CH_3)CHOH$	IIL	0.60 (3, 4, 6, 7)[a]	1.00
$(C_{0.5n})_2CHOH$	IIE	0.57 (4, 6, 8)[a]	0.95
$C_n(C_4)CHOH$	IIS	0.54 (1, 2, 4)[a]	0.90
		Ester	
CH_3COOC_n	IIL_1	0.63 (1-3),[c] 0.61 (2-5),[d] 0.508[b]	
C_3COOC_n	IIS_1	0.56 (1-3),[c] 0.55 (1-3),[d] 0.552[b]	
$C_{0.5n}COOC_{0.5n}$	IIE	0.606 (1, 3)[c]	
C_nCOOC_2	IIL_2	0.68 (2-4, 7),[d] 0.50 (3-6),[c] 0.500[b]	
C_nCOOC_5	IIS_2	0.35 (1-3)[d]	
		Ethyleneglycol Diester	
$(CH_2OCO_{0.5n})_2$	IIE	0.53 (2, 4, 6, 8)[e]	
		Triglyceride	
	IIIE	0.48 (3, 6, 9, 15)[f]	

[a] Taken from ref 41. [b] Taken from ref 7. [c] Taken from ref 40. [d] Taken from ref 42. [e] Taken from ref 3. [f] Taken from ref 4.

For most of the compounds shown in Table I, $a_I \geq a_{IIL} > a_{IIE} > a_{IIS}$. As Figure 1 illustrates, the difference between types is smaller in Figure 1b than in Figure 1a. This is due to alkyl chain branching correction when its partition coefficient is estimated. In general, the presence of branching in an aliphatic chain produces a reduction in the partition coefficient as compared to the straight-chain isomer. Leo et al. have suggested a log P value of −0.20 for branching.[37] Branching due to a functional group also appears to lower the partition coefficient by the same amount.[38]

The difference between types, however, still exists in Figure 1b. For most of the compounds shown in Table I, $A_I \geq A_{IIL} > A_{IIE} > A_{IIS}$. This is at least partly due to not taking into consideration a reduction of the partition coefficient responsible for the intramolecular association of double chains in water. The value of a/a_I, rather than a itself, reflects the decreased hydrophobicity of double-chain compounds, since a_I depends on the biological activity investigated.

Parabolic Relationships. As log P values become larger or the time of the experiment becomes shorter, a linear relationship (eq 4 or 5) is not the rule, and one finds a much better correlation by a second-order equation, e.g., eq 3.[6,7] This equation holds not for a simple system, such as protein binding, but for rather complicated systems, such as whole animals. This type of equation, therefore, has been rationalized by considering the movement of the drug from the point of introduction to the active sites through a series of compartments.[6,7,39]

An example conforming with eq 3 is shown in Figure 2. In Table I are included the optimum number (n_{op}) of carbon atoms and the optimum partition coefficient (P_{op}), which correspond to the maxima in Figure 2a and 2b, respectively. In Figure 2, C denotes the duration (in minutes) of the depressant effect of ethyl barbiturates, n is the number of carbon atoms in a substituted alkyl chain, and most of the P values are calculated on the basis of the "additivity" rule of log P, by using the observed P value of a barbiturate. As Figure 2 shows, different types of barbiturates lie on different lines. Similar results are obtained for other drugs, as shown in Table I. For all drugs investigated, $n_{opI} < n_{opIIL} < n_{opIIE}$, and $P_{opI} < P_{opIIL} < P_{opIIE}$. The difference between types is slightly smaller in Figure

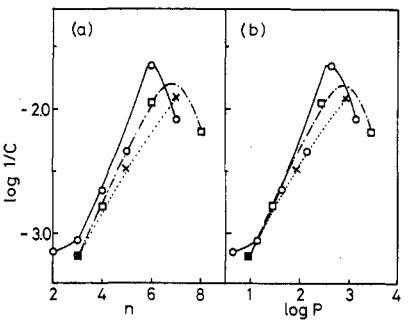


Figure 2. The logarithm of duration (minutes) (C) of the depressant effect of barbiturates (19, Table I) as a function of the number of carbon atoms of an alkyl chain (a), and log P (b): types I, solid line; IIL, dot-dash line; IIE, dotted line.

Table III. Negative Slopes of Log cmc vs. n Plots for Double-Chain Compounds

compd	type	a (investigated n)[a]	a/a_I
		Sulfoxide	
CH_3SOC_n	IIL_1	0.58 (6-12)	
C_2SOC_n	IIL_2	0.57 (8, 10)	
C_8SOC_n	IIS_1	0.27 (1-3)	
$C_{10}SOC_n$	IIS_2	0.19 (1, 2)	
		Sodium Alkyl Sulfate	
C_nSO_4Na	I	0.29 (8, 12, 14, 16, 18)	1.00
$C_nCH(SO_4Na)C_m$	IIL	0.26-0.29 (varies)	0.90-1.0
$C_{0.5n}CH(SO_4Na)C_{0.5n}$	IIE	0.24 (10, 12, 14, 16, 18)	0.83
$C_nCH(SO_4Na)C_m$	IIS	0.14-0.19 (varies)	0.48-0.66

[a] Taken from ref 2.

Table IV. Slopes of Log P vs. n Plots for Double-Chain Compounds

compd	type	a (investigated n)	a/a_I	a/a_{IIL}
		Alcohol		
C_nOH	I	0.57 (1-6, 8)[a]	1.00	
$C_n(C_2)CHOH$	IIS	0.27 (0, 1)[a]	0.47	
		Ester		
CH_3COOC_n	IIL	0.55 (1, 2)[b,c]		1.00
$C_{0.5n}COOC_{0.5n}$	IIE	0.52 (2,4)[b]		0.95
C_nCOOC_2	IIS	0.48 (1, 2)[b,c]		0.87
		Amphetamine		
$-NHC_n$	I	0.62 (1-4)[d]	1.00	
$-N(CH_3)C_n$	IIL	0.71 (1-5)[d]	1.15	
$-N(C_{0.5n})_2$	IIE	0.73 (2, 4, 6, 8)[d]	1.18	
$-N(C_4)C_n$	IIS	0.80 (1, 4)[d]	1.29	
		Alkylamine		
C_nNH_2	I	0.48 (1, 4)[a]	1.00[a]	
C_nNHCH_3	IIL	0.60 (3-5)[e]		1.00[e]
$NH(C_{0.5n})_2$	IIE	0.50 (4, 6, 8),[a] 0.62 (4, 6, 8)[e]	1.04[a]	1.03[e]
C_4NHC_n	IIS	0.45 (1, 4),[a] 0.63 (1-4)[e]	0.94[a]	1.05[e]

[a] Original data taken from ref 37b. [b] Taken from ref 43. [c] Taken from ref 44. [d] Heptane-water phases; taken from ref 30. [e] Cyclohexane-water phases; taken from ref 45.

(37) (a) A. Leo and C. Hansch, *J. Org. Chem.*, **36**, 1539 (1971). (b) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
(38) C. Hansch, in "Drug Design", Vol. 1, E. J. Ariens, Ed., Academic Press, New York, 1971, p 271.
(39) (a) H. Kubinyi, *Arzneim.-Forsch.*, **26**, 1991 (1976). (b) H. Kubinyi, *J. Med. Chem.*, **20**, 625 (1977).

2b than in Figure 2a, since the correction of branching in the partition coefficient estimation has been done in Figure 2b.

Physicochemical Properties of Double-Chain Compounds. The solubility and cmc of a substance in water, as well as the partition coefficient, are measures of the hydrophobicity. For several double-chain compounds, the slopes (a) of log C_s, log cmc, and log P vs. n plots are shown in Tables II–IV. From the thermodynamic viewpoint, when the solubilities of a substance in water (C_s) and in 1-octanol (C_{so}) are small, we can expect eq 6 for the partition coefficient. Using this equation, we can explain that the a values in Tables II and IV are almost equal for each type. Hansch et al. showed almost proportional relations of P to C_s for many compounds.[40]

$$\log P = -\log C_s + \log C_{so} \quad (6)$$

As Tables II–IV show, the slope (a) depends on the type, except for alkyl amines and amphetamines: $a_I \geq a_{IIL} > a_{IIE} > a_{IIS}$. This order is consistent with that observed for biological activities. The a value of sodium alkyl sulfate is smaller than the values of nonelectrolytes, but the a/a_I value does not appear to depend on electrolyte or nonelectrolyte. This has been discussed elsewhere.[2]

Hermann showed that the water solubility of a hydrocarbon is correlated with the solute surface area better than with the molar volume of the solute or the number of carbon atoms.[46] According to his viewpoint, increased solubility of the branched-chain compounds relative to the straight-chain isomers was attributed to a smaller effective surface area. This theory has been extended to amphiphilic compounds.[41] Further, the increased C_s or cmc values of the double-chain compounds relative to the single-chain compounds shown in Tables II and III have been ascribed to a decreased surface area of double-chain compounds caused by the intramolecular association in water.[2-5] The magnitude of a for the double-chain compounds is explicable on the basis of an increase in the water contact area accompanying the addition of one methylene group, taking into consideration the intramolecular association between two alkyl chains in water. Since the methylene group added to the longer chain (type IIL) does not come into contact with the shorter chain on the same molecule, the a value for type IIL is almost equal to that for type I. Since in the type IIE compound a part of the surface area of an added methylene group is covered by the other chain, the value of a for type IIE is smaller than that for type IIL. On the other hand, in the type IIS compound, the methylene group added to the shorter chain associates with the longer chain in contact with water, and the a value for type IIS is smaller than that for type IIE.

As Table IV shows, the partition coefficient for aliphatic alkylamines[37b,45] and amphetamine derivatives[30] does not appear to depend on the type, probably due to the lack of the intramolecular association of the two alkyl chains in water.

The difference in strength of biological activity among the types shown in Table I may be explained, at least partly, by the intramolecular association of a double-chain drug in water, viz., a decreased hydrophobicity relative to a single-chain isomer.

Discussion

Prior to discussing the structure–activity relationships, let us consider the physicochemical properties of double-chain compounds. As Tables II–IV show, two alkyl chains of at least some double-chain compounds associate intramolecularly in water. Proton nuclear magnetic resonance data also suggested the intramolecular association of two alkyl chains of dialkyl sulfosuccinate in water.[47] On the other hand, the slope of log P vs. n plots for dialkylamines and amphetamine derivatives is almost equal to that of the corresponding monoalkyl compounds (Table IV), suggesting that the two alkyl chains of these compounds do not associate intramolecularly in water. The degree of intramolecular association of double-chain compounds is expected to depend on the distance and steric angle between the two chains on a molecule. These factors will be determined by the kind of the group connecting the chains and should affect the a/a_I value. The effect of the connecting group on the a/a_I value needs further investigation because of inaccuracy and deficiency of the available data shown in Tables II–IV. Further, longer chain compounds might tend to associate more.

The parameters for representing the structure–activity relationships depend on the type, as shown in Table I. For most compounds, $A_I \geq A_{IIL} > A_{IIE} > A_{IIS}$, and $P_{opI} < P_{opIIL} < P_{opIIE}$. This result contradicts with eq 3 and 5, since these equations predict that the strength of the biological activity of homologues depends solely on their partition coefficients, regardless of the type. This disagreement may be ascribed to two factors.

First, most partition coefficient data are not experimentally determined but calculated by the additivity of group contributions to log P; e.g., the methylene group contribution is assumed to be 0.5 regardless of types. This is valid for single-chain compounds but is too large for at least some double-chain compounds.

The second is the steric factor. This factor was neglected in the present work, since only comparison among homologues was made. Some biological activities, however, can be affected by the steric factor, even if only the alkyl chain length changes. For all amphetamine derivatives analyzed in Table I, their partition coefficients were measured. Nevertheless, values of A are dependent on types. Amphetamines are attacked by an enzyme to yield the corresponding N-dealkylated products. In Table I, the percentage of an excreted amphetamine unchanged is given as a biological activity. In this case, the dealkylation of amphetamines by the enzyme will depend on the bulk of the amine moiety, viz., the number and length of an alkyl group(s). The affinity of amphetamines to the enzyme can be adequately estimated by the partition coefficient, but the steric factor due to the bulky alkyl group is not taken into consideration by it. The same factor may play a role in some biological activities for other compounds, including single- and double-chain compounds.

When the linear relationship, eq 4, holds, it is interesting to compare biological activity with physicochemical properties. For each type, the a/a_I values of all drugs shown in Table I, except for 8, 11, and 17, are close to those shown in Tables II–IV (excluding alkylamines and

(40) C. Hansch, J. E. Quinlan, and G. L. Lawrence, *J. Org. Chem.*, **33**, 347 (1968).
(41) G. L. Amidon, S. H. Yalkowsky, and S. Leung, *J. Pharm. Sci.*, **63**, 1858 (1974).
(42) N. C. Deno and H. E. Berkheimer, *J. Chem. Eng. Data*, **5**, 1, (1960).
(43) C. Hansch and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).
(44) S. C. Valvani, S. H. Yalkowsky, and T. J. Roseman, *J. Pharm. Sci.*, **70**, 502 (1981).
(45) I. H. Pitman, K. Uekama, T. Higuchi, and W. E. Hall, *J. Am. Chem. Soc.*, **94**, 8147 (1972).
(46) R. B. Hermann, *J. Phys. Chem.*, **76**, 2754 (1972).
(47) M. Ueno, H. Kishimoto, and Y. Kyogoku, *Chem. Lett.*, 599 (1977).

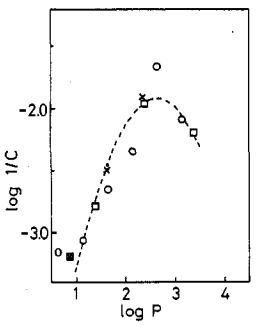


Figure 3. The logarithm of duration (minutes) (C) of the depressant effect of barbiturates (**19**, Table I) as a function of the logarithm of corrected partition coefficients: (○) types III_1; (□) III_2; (x) IIE. The dashed line is calculated from the parabolic equation: $\log (1/C) = -0.511(\log P)^2 + 2.706 \log P - 5.495$.

amphetamines), suggesting that these cases can be explained solely by the hydrophobicity factor correction. For these cases, therefore, the difference in A/A_I between types is responsible for an inadequate estimation of partition coefficients. For the exceptional cases mentioned above there are too few experimental data (Table I) to draw any conclusions. The negative a values of **32** and **33** in Table I probably correspond to the large P region in the parabolic equation.

The correction of a decreased hydrophobicity of double-chain compounds is also important, when the parabolic equation holds. Such an example is shown in Figure 3. In this figure, partition coefficients of types III_2 and IIE of ethyl barbiturates (**19** in Table I) are corrected, employing the observed P value of diethyl barbiturate and assuming that a_{IIS}/a_{IIL1} is equal to a_{IIS}/a_I for type IIS alcohols in Table IV, viz., 0.47. The type dependence seen in Figure 2 disappears in Figure 3.

As relevant structure–activity data are compiled hereafter, the accuracy of prediction will be improved, and applications of the present approach will be extended for various double-chain compounds and various biological activities. The present work is expected to be useful also for predicting the partition coefficients of double-chain compounds, designing drugs, and elucidating the mechanism of pharmacological action of drugs.

Registry No. Butyrylcholinesterase, 9001-08-5.

Inhibition of Prostaglandin Synthetase by Di- and Triphenylethylene Derivatives: A Structure–Activity Study

Jacques Gilbert,[†] Jean-François Miquel,*[,†] Gilles Précigoux,[‡] Michel Hospital,[‡] Jean-Pierre Raynaud,[§] Françoise Michel,[⊥] and André Crastes de Paulet[⊥]

Centre d'Etudes et de Recherches de Chimie Organique Appliquée, CNRS, associé à l'ENSCP, 94320 Thiais, Laboratoire de Cristallographie et de Physique Cristalline, associé au CNRS, Université de Bordeaux I, 33405 Talence, Roussel-Uclaf, 75007 Paris, Unité de Recherches sur la Biochimie des Stéroïdes, INSERM U58, 34100 Montpellier, France. *Received June 9, 1982*

The syntheses of new di- and triphenylethylene derivatives are described along with their X-ray analysis and NMR study, which have helped to establish their conformation. Screening of over 50 derivatives for inhibition of prostaglandin synthetase (PGS) activity in bovine seminal vesicle microsomes has revealed that many of the triphenylethylene derivatives are potent inhibitors of PGS. Several even show marked activity at the extremely low concentration (IC_{50}) of about 4×10^{-8} M, which is two orders of magnitude lower than the active concentration of the majority of known nonsteroidal antiinflammatory agents ($IC_{50} \approx 10^{-6}$ M). Unlike the latter, these compounds are not carboxylic acids. Furthermore, in contrast to biphenyl, diphenylmethane, or unsymmetrical, α,α'-diphenylethylene PGS inhibitors, the presence of a β-phenyl ring was an essential requirement for high potency. The best inhibitors possessed a cyanide group (acids, amides, and amines were poor inhibitors), methoxy in preference to hydroxy groups on the α-phenyl rings, and a halogen (F or Cl) in a para position on the β-phenyl ring. These data provide additional insight into the nature of the PGS binding site.

Several triphenylethylene-derived (TPE) compounds, such as clomiphene [1-[*p*-[β-(diethylamino)ethoxy]-phenyl]-1,2-diphenyl-2-chloroethylene], tamoxifen [1-[*p*-[β-(dimethylamino)ethoxy]phenyl]-1,2-diphenylbut-1-ene], and MER-25 [1-[*p*-[2-(diethylamino)ethoxy]-phenyl]-1-phenyl-2-(*p*-methoxyphenyl)ethanol], are known for their antiestrogenic properties and are used clinically for ovulation induction,[1] for the treatment of hormone-dependent cancers,[2] and for diagnostic purposes.[3] However, some of these compounds have also been shown to inhibit prostaglandin synthetase (PGS), and, according to a few authors, this enzyme inhibition could explain part of their biological effects.[4-7]

In a previous study,[8] we reported the synthesis of cyano derivatives of TPE's with affinity for the cytosol estrogen receptor. In the present paper, we describe the synthesis of new derivatives in this series and the results of a structure–activity study on over 50 compounds, in which inhibition of PGS has been measured in bovine seminal

[†] CERCOA, CNRS.
[‡] Université de Bordeaux I.
[§] Roussel-Uclaf.
[⊥] Unite de Recherches sur la Biochimie des Steroïdes.

(1) A. Klopper and M. Hall, *Br. Med. J.*, 1, 152-154 (1971).
(2) S. S. Legha and S. K. Carter, *Cancer Treat. Rev.*, 3, 205-216 (1976).
(3) M. G. R. Hull, M. A. F. Murray, S. Franks, B. A. Lieberman, and H. S. Jacobs, In "The Endocrine Function of the Human Ovary", V. H. T. James, M. Serio, and G. Giusti, Eds., Academic Press, New York, 1976, pp 245-259.
(4) L. J. Lerner, P. Carminati, and P. Schiatti, *Proc. Soc. Exp. Biol. Med.*, 148, 329-332 (1975).
(5) S. C. Sharma and D. M. Pugh, *Eur. J. Pharmacol.*, 42, 91-92 (1977).
(6) L. Fenwick, R. L. Jones, B. Naylor, N. L. Poyser and N. H. Wilson, *Br. J. Pharmacol.*, **59**, 191-199 (1977).
(7) V. D. Castracane and V. C. Jordan, *Prostaglandins*, 12(2), 243-251 (1976).
(8) J. F. Miquel, A. Sekera, and T. Chaudron, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **286**, 151-154 (1978).

0022-2623/83/1826-0693$01.50/0