TABLE III

5′-Ester	Composition	Reaction solvent	Recrystn solvent	Mp, °C	Yield, %	Analyses
Palmitoyl	$C_{25}H_{43}N_3O_6$	DMA	MeOH	147–149	80	C, H, N
Octanoyl	$C_{17}H_{27}N_3O_6$	DMF	EtOAc	158–161	55	C, H, N
Acetyl	$C_{11}H_{15}N_3O_6$	DMF	*n*-BuOH	184–185	38	C, H, N
Pivaloyl	$C_{14}H_{21}N_3O_6$	DMA	*n*-BuOH	260–261	55	C, H, N
Benzoyl	$C_{16}H_{17}N_3O_6 \cdot H_2O$	DMA	*n*-BuOH[a]	205–206	77	C, H, N[b]
Cyclohexylcarbonyl	$C_{16}H_{23}N_3O_6$	DMF	EtOAc	232 dec	53	C, H, N
1-Adamantoyl	$C_{20}H_{27}N_3O_6$	DMA	EtOAc	291 dec	70	C, H, N
3-Quinuclidinoyl[c]	$C_{17}H_{24}N_4O_6 \cdot 2HCl$	DMA	EtOH	188 dec	55	C, H, N, Cl

[a] After soln in hot BuOH, addn of 2–3% of H_2O induced rapid crystn. [b] Anal. for the anhyd material; when dried at 60° *in vacuo*, the wt loss was 4.82% (calcd for 1 H_2O: 4.93%). [c] Prepd using rac quinuclidine-3-carboxylic acid; isolated as the di·HCl by crystn from the reaction mixt.

fractions. The residue was dissolved in MeOH, 3 g of Zn dust was added, and the mixt was refluxed for 15 min. The 5′-ester so obtained was purified by chromatog over silica gel, eluting with MEK–Me_2CO–H_2O (72:20:8). The purified 5′-ester was recovered by evapn *in vacuo* of pooled fractions and recrystd. Results and anal. data are summarized in Table II.

In the cases of the 2,6-dimethylbenzoyl, β-chloropivaloyl, and (3-carboxymethyl-adamantane-1)acetyl esters, a considerable amt of unreacted N^4-trichloroethoxycarbonyl ara-C remained after treatment with the acid chloride. Further treatment with up to a 1 mole excess of these sterically hindered acid chlorides effected more nearly complete reaction without significant reaction at the 2′ or 3′ position.

Direct Synthesis of 5′-Esters of Ara-C.—The HCl of ara-C (0.01 mole) was dissolved in 25 ml of DMF or suspended in 50 ml of DMA, 0.011 mole of the acid chloride was added, and the mixt was stirred overnight at room temp. In the cases of the prepn of the 5′-benzoyl and 5′-adamantoyl esters, a second portion of the acid chloride was added and the reaction was allowed to continue for an addnl 24 hr. The reaction mixt was concd *in vacuo* to an oil, and the oil was thoroughly triturated with EtOAc–Et_2O (1:1). The oil was then thoroughly triturated with 1 *N* $NaHCO_3$. The cryst solid was collected, washed several times with H_2O, and dried. One recrystn yielded the pure ester. Results and anal. data are summarized in Table III.

Because of its soly in H_2O, the 5′-acetyl ester could not be purified as described above. After concn of the reaction mixt, the resultant oil was first triturated with Et_2O and then dissolved in H_2O. The pH was adjusted to 1.5, and the soln was extd several times with equal vols of EtOAc. The pH of the aq soln was then adjusted to 7, and the solvent was evapd *in vacuo*. The oil was dissolved in EtOH, and the NaCl was removed by filtn. The solvent was evapd *in vacuo* to leave an oil. The crude product was purified by chromatog over silica gel, using MEK–Me_2CO–H_2O (72:20:8) as the solvent. The purified ester had a mp of 184–185°, and was apparently obtained in an anhyd form, in contrast to the hemihydrate previously obtained for this ester [mp 115–117.5° (Table II)].

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Quantitative Structure–Activity Relationships in Leucomycin and Lincomycin Antibiotics

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The *in vitro* antibacterial activity of members of the leucomycin complex increase with increasing partition coefficient and removal of esterification of the 3 hydroxyl of the macrolide ring. In the series of 25 NCH_3 and NC_2H_5 lincomycins an optimum log *P* of 1.1 was calculated for *in vitro* activity *vs. Sarcina lutea* and 0.4 for *in vivo* activity *vs Staphylococcus aureus*. The *in vitro* activity of the NH lincomycins is positively correlated with log *P* (optimum >2.7). Electronic and steric factors also influence the activity of these antibiotics. An optimum partition coefficient is indicated in the clindamycins.

The antibiotics lincomycin and leucomycin are both considered to act by binding to the 50S ribosome to prevent bacterial protein synthesis. The relative *in vitro* antibacterial activity of various individual members of the leucomycin complex has recently been reported.[1] Similarly, the activity of a large number of alkyl analogs of lincomycin has been studied by Magerlein, *et al.*[2–4] It was our interest to investigate the quantitative structure–activity relationships in each series of compounds and to compare the results from these studies to form a general concept of the patterns which govern activity in this type of molecule. For this purpose the extrathermodynamic approach to structure–activity studies[5] was used.

Experimental Section

Partition Coefficients.—The π values [change in the logarithm of the 1-octanol–H_2O partition coefficient (log *P*) of a derivative compared to the parent compound] were calcd as outlined by Iwasa, *et al.*[5]

The log *P* value of leucomycin A1 (compound 1 in Table II) was calcd from the experimental observation of the log *P* value

(1) S. Omura, M. Katagiri, I. Umezana, K. Komiyama, T. Maekawa, K. Sekikawa, A. Matsumae, and T. Hata, *J. Antibiot.*, **21**, 532 (1968).

(2) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Med. Chem.*, **10**, 355 (1967).

(3) B. J. Magerlein and F. Kagan, *ibid.*, **12**, 780 (1969).

(4) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *Antimicrob. Ag. Chemother.*, **1966**, 727 (1967).

(5) J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, **8**, 150 (1965).

for niddamycin[6] of 1.86.† Niddamycin and leucomycin A1 differ only at C9 in the macrolide ring; in the former the group is C=O, in the latter it is OH. The π value for this change was calcd from the log P values of 2-butanone and 2-BuOH which were 0.29 and 0.61, respectively.[7] Thus the approximate log P value of leucomycin A1 is 1.86 + 0.61 − 0.29 or 2.18.

The actual partition coefficients for 3 of the lincomycins have been reported.[4] These values, plus the log P of the uncharged molecule calcd from the observed log P, the pK_a (7.2 ref 8), and the pH of measurement are also listed in Table I. From this

TABLE I

OCTANOL–WATER PARTITION COEFFICIENTS (P) OF N-METHYL LINCOMYCIN DERIVATIVES

4′ Substitution	P at pH 7.0	P of uncharged form[a]	log P	π compared to one less carbon
C_2H_5	0.08	0.40	−0.40	
C_3H_7	0.32	1.60	0.20	0.60
C_4H_9	0.73	3.65	0.56	0.36
C_5H_{11}	1.69	8.45	0.93	0.37
			Mean	0.44

[a] Calcd from the observed P, the pH of observation, and the pK_a by the use of A. Albert, "Selective Toxicity," Methuen, London, 1965, p 346.

table it can be seen that the mean π_{CH_2} is 0.44. However the standard 0.5 was used for this π value.

Activities.—The reported antimicrobial activities were adjusted for differences in mol wt.

Statistical Analyses.—These anal. were performed using stepwise multiple regression on an IBM 1800 computer.[9] The 95% confidence limits for optimum π values were calcd according to ref 10.

Results

Leucomycin Series. The structures and relative antibacterial activity of the compounds *vs. Bacillus subtilis* are listed in Table II. It can be seen that the

TABLE II

In Vitro ACTIVITY OF LEUCOMYCINS *vs. B. subtilis*

No.	R	R′	π'	Log relative antibacterial activity Obsd[a]	Calcd[b]
1	H	$OCOCH_2CH(CH_3)_2$	1.80	3.22	3.31
2	$COCH_3$	$OCOCH_2CH(CH_3)_2$	1.80	3.09	3.10
3	H	$OCOCH_2CH_2CH_3$	1.50	3.18	3.19
4	$COCH_3$	$OCOCH_2CH_2CH_3$	1.50	3.00	2.98
5	H	$OCOCH_2CH_3$	1.00	3.10	2.98
6	$COCH_3$	$OCOCH_2CH_3$	1.00	2.89	2.77
7	H	$OCOCH_3$	0.50	2.75	2.77
8	$COCH_3$	$OCOCH_3$	0.50	2.43	2.56

[a] Ref 1. [b] Eq 2.

compounds can be separated into 2 subseries, those with the 3-OH of the lactone ring acetylated and those with it free. The other difference between the molecules is the length of hydrocarbon chain on the O-acyl group of the mycarose. These latter changes on the molecule produce a 3- to 4- fold change in activity. This suggests that the relative antibacterial activity is dependent on the lipophilic nature of the molecule.

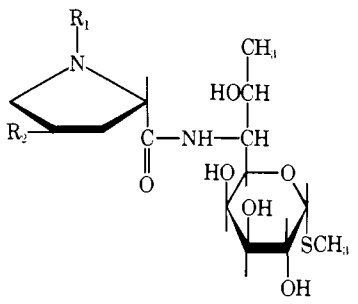
The changes at the two positions were considered separately since the π value for the change from OH to OAc_3 could be estimated less accurately than the corresponding values for hydrocarbon changes.[5,7] Thus the regression equations included the π value for the hydrocarbon chain of the O-acyl group and a dummy variable Ac which would include the change in steric, lipophilic, or H-bonding factors for the change from 3-OH to 3-OAc. Equations 1 and 2 resulted from this analysis. The coefficients plus or minus standard deviations are given. n is the number of compounds, r is the correlation coefficient, s is the standard deviation, and F is the test of statistical significance of the overall equation. In eq 2 Ac is significant at the 95% confidence level.

	n	r	s	$F_{1,6}$	
log act = 2.458 + 0.416π (±0.111)	8	0.837	0.155	14.13	(1)
log act = 2.563 + 0.416π − 0.210Ac (±0.076) (±0.075)	8	0.940	0.105	19.09	(2)

From these equations it can be seen that for the leucomycin series the relative antibacterial activity of a compound is positively correlated with the π value for the substituent on the mycarose. Steric factors (Taft E_s values) for substituents at this position were not related to activity either alone or in combination with π values. In addition the acetylated compounds are *less* active by a factor of 1.6 than the analogous free compounds. Since π would be expected to *increase* on acetylaion, either steric or H-bonding factors must increase the activity of the unsubstituted (OH) compounds.

Thus if there is an optimum log P in this series it is probably 2.18 or higher.

Lincomycins. *In Vitro*—In the parallel analysis of the *in vitro* activity of the lincomycin analogs against *Sarcina lutea* the π value was again used for hydrophobic activity and the various subseries of compounds were examined separately and in combination. The data which were used in the analysis are listed in Table III



lincomycin

and the structure of lincomycin is given below. The equations which resulted from this analysis are listed in Table IV.

In these equations T is a dummy variable which has a value of 1.0 for trans-substituted compounds and zero for cis substitution. Et is a dummy variable which is 1.0 when R_1 is C_2H_5 and zero when R_1 is CH_3.

(6) G. Huber, K. H. Wallhausser, L. Fries, A. Steigler, and H. Wiedenmüller, *Arzneimittel.-Forsch.*, **12**, 1191 (1962).

† The authors thank J. Theriault for the sample of niddamycin and R. Cantrell for the experimental determination of its log P value.

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(8) D. J. Mason, A. Dietz, and C. Deboer, *Antimicrob. Ag. Chemother.*, **1962**, 554 (1963).

(9) N. R. Draper and H. Smith, "Applied Regression Analysis," Wiley, New York, N. Y., 1966, p 119.

(10) A. Hold, "Statistical Theory with Engineering Applications," Wiley, New York, N. Y., 1952, p 654.

TABLE III

In Vitro ACTIVITY OF LINCOMYCINS *vs. S. lutea*

R'1	R'2		π	Relative activity Obsd[a]	Relative activity Calcd	
H	H		−0.50	−0.146	−0.251	Eq 10
H	n-C_3H_7	Cis–trans	1.00	0.104	0.263	Eq 10
H	n-C_4H_9	Cis–trans	1.50	0.391	0.434	Eq 10
H	n-C_5H_{11}	Cis–trans	2.00	0.552	0.605	Eq 10
H	n-C_6H_{13}	Cis–trans	2.50	0.880	0.776	Eq 10
H	n-C_7H_{15}	Cis–trans	3.00	1.020	0.947	Eq 10
H	n-C_8H_{17}	Cis–trans	3.50	1.090	1.118	Eq 10
CH_3	H		0.00	−0.164	−0.413	Eq 9
CH_3	n-C_2H_5	Trans	1.00	0.882	0.964	Eq 9
CH_3	n-C_3H_7	Trans	1.50	1.390	1.355	Eq 9
CH_3	n-C_4H_9	Trans	2.00	1.697	1.625	Eq 9
CH_3	n-C_5H_{11}	Trans	2.50	1.892	1.774	Eq 9
CH_3	n-C_6H_{13}	Trans	3.00	1.903	1.802	Eq 9
CH_3	n-C_7H_{15}	Trans	3.50	1.510	1.709	Eq 9
CH_3	n-C_8H_{17}	Trans	4.00	1.321	1.494	Eq 9
CH_3	n-C_3H_7	Cis	1.50	1.089	1.124	Eq 9
CH_3	n-C_4H_9	Cis	2.00	1.489	1.394	Eq 9
CH_3	n-C_5H_{11}	Cis	2.50	1.616	1.543	Eq 9
CH_3	n-C_6H_{13}	Cis	3.00	1.669	1.570	Eq 9
CH_3	n-C_7H_{15}	Cis	3.50	1.288	1.477	Eq 9
CH_3	n-C_8H_{17}	Cis	4.00	1.099	1.263	Eq 9
C_2H_5	H		0.50	−0.277	0.018	Eq 9
C_2H_5	n-C_3H_7	Trans	2.00	1.375	1.422	Eq 9
C_2H_5	n-C_4H_9	Trans	2.50	1.440	1.572	Eq 9
C_2H_5	n-C_5H_{11}	Trans	3.00	1.824	1.599	Eq 9
C_2H_5	n-C_6H_{13}	Trans	3.50	1.635	1.506	Eq 9
C_2H_5	n-C_8H_{17}	Trans	4.50	0.910	0.956	Eq 9
C_2H_5	n-C_3H_7	Cis	2.00	1.074	1.191	Eq 9
C_2H_5	n-C_4H_9	Cis	2.50	1.206	1.340	Eq 9
C_2H_5	n-C_5H_{11}	Cis	3.00	1.461	1.368	Eq 9
C_2H_5	n-C_6H_{13}	Cis	3.50	1.413	1.274	Eq 9
C_2H_5	n-C_8H_{17}	Cis	4.50	0.910	0.725	Eq 9

[a] Ref 2.

from subseries to subseries. It is approximately 2.7 or an optimum log P of 1.1.

Also, the coefficient of the dummy variable T is rather constant from equation to equation. This indicates that trans compounds are on the average 1.7 times as active as the corresponding cis compound, an observation previously noted by Magerlein.[2] This effect is not a result of a systematic deviation of π values for trans *vs.* cis compounds. Such a deviation would result in different effects depending on the position of the various compounds with respect to the optimum log P. The greater activity of the trans compounds seems to be most likely a generalized structural or steric effect.

From the coefficient of the dummy variable Et one may calculate that the N-Et compounds are on the average 1.6 times less active than the corresponding N-Me derivatives with the same number of total C atoms. Again the effect is not a partition coefficient effect, but rather a steric or electronic effect.

The activities of the compounds in which the amino group is unsubstituted are summarized by the relationship in eq 10. For these compounds the optimum log P was not reached at a π value of 3.5 which is higher than the optimum calcd for the previous compounds.

Lincomycins. *In Vivo.*—The data used in these calculations are listed in Table V. Equation 11 resulted from this analysis. Both terms are statistically

	n	r	s	F	
log potency = 0.530 + 0.854π − 0.198π^2 ($\pm$0.074) ($\pm$0.013)	11	0.992	0.046	264	(11)

significant. The optimum π value for *in vivo* activity against *Staphyloccous aureus* is thus calcd to be 2.16 ($\pm$0.050) or 0.71 log units lower than the *in vitro* optimum with *Sarcina lutea* (Table IV).

TABLE IV

EQUATIONS WHICH RELATE *in Vitro* ACTIVITY OF LINCOMYCIN ANALOGS TO PHYSICAL PROPERTIES

	n	r	s	F	π° [a]	Eq
N-Methyl Derivatives						
log act = −0.238 + 1.458π − 0.274π^2 ($\pm$0.133) ($\pm$0.029)	14	0.961	0.155	68.27	2.66 ($\pm$0.209)	3
log act = −0.282 + 1.402π − 0.262π^2 + 0.196T ($\pm$0.102) ($\pm$0.022) ($\pm$0.064)	14	0.980	0.117	83.51	2.67 ($\pm$0.171)	4
N-Ethyl Derivatives						
log act = −0.308 + 1.448π − 0.284π^2 ($\pm$0.144) ($\pm$0.032)	11	0.963	0.167	51.76	2.55 ($\pm$0.247)	5
log act = −0.527 + 1.528π − 0.298π^2 + 0.228T ($\pm$0.103) ($\pm$0.022) ($\pm$0.073)	11	0.984	0.115	75.62	2.56 ($\pm$0.153)	6
N-Methyl Plus *N*-Ethyl Derivatives						
log act = −0.439 + 1.450π − 0.256π^2 ($\pm$0.147) ($\pm$0.078)	25	0.914	0.226	56.08	2.83 ($\pm$0.248)	7
log act = −0.474 + 1.383π − 0.245π^2 + 0.244T ($\pm$0.122) ($\pm$0.024) ($\pm$0.078)	25	0.942	0.191	55.12	2.82 ($\pm$0.226)	8
log act = −0.413 + 1.388π − 0.242π^2 + 0.232T − 0.203Et ($\pm$0.103) ($\pm$0.0205) ($\pm$0.066) ($\pm$0.067)	25	0.960	0.162	60.21	2.87 ($\pm$0.193)	9
NH Derivatives						
log act = −0.080 + 0.342π ($\pm$0.033)	7	0.977	0.107	109.78	>3.5	10

[a] π° is the optimum value of π giving greatest *in vitro* activity.

From eq 3, 5, and 7 it can be seen that an excellent statistical fit of the relative antimicrobial activity of the N-Me compounds is obtained by using the empirical parameter π. The calcd optimum π is rather constant

Clindamycins. *In Vitro.*—Clindamycin is an antibiotic derived from lincomycin by substitution of Cl

TABLE V

In Vivo POTENCY OF LINCOMYCIN ANALOGS *vs.* *S. aureus* INFECTIONS

R	R′	Potency in mouse protection test Obsd[a]	Calcd[b]
CH_3	C_2H_5	1.17	1.19
CH_3	C_3H_7	1.39	1.37
CH_3	C_4H_9	1.45	1.45
CH_3	C_5H_{11}	1.49	1.43
CH_3	C_7H_{15}	1.04	1.10
CH_3	C_8H_{17}	0.80	0.78
C_2H_5	C_3H_7	1.38	1.45
C_2H_5	C_4H_9	1.48	1.43
C_2H_5	C_5H_{11}	1.30	1.31
C_2H_5	C_6H_{13}	1.07	1.10
C_2H_5	C_8H_{17}	0.39	0.37

[a] Ref 2. [b] Eq 11.

for the OH group at C_7 of the parent. The stereochemistry at this atom is in opposite configurations in the two molecules. The compounds which were included in this analysis are listed in Table VI. The organism

TABLE VI

In Vitro ACTIVITY OF *N*-DESMETHYL CLINDOMYCINS *vs.* *S. lutea*

R′	π	Relative activity Obsd[a]	Calcd[b]
C_2H_5	1.0	−0.046	0.034
n-C_3H_7	1.5	0.602	0.481
n-C_4H_9	2.0	0.699	0.679
n-C_5H_{11}	2.5	0.602	0.626
n-C_6H_{13}	3.0	0.255	0.324
n-C_8H_{17}	4.0	−1.000	−1.030

[a] Ref 3. [b] Eq 12.

used was *S. lutea*.

Equation 12 describes these relationships. The

	n	*r*	*s*	*F*	
log act = $-1.61 + 2.145\pi - 0.500\pi^2$ (± 0.213) (± 0.042)	6	0.993	0.095	111.33	(12)

optimum π value is 2.14 (±0.075).

Clindamycins. *In Vivo.*—An analogous analysis of the *in vivo* activity of these compounds against *S. aureus* (Table VII) was performed. For the derivatives in which the amino group is unsubstituted eq 13

	n	*r*	*s*	*F*	
log potency = $0.254 + 1.55\pi - 0.365\pi^2$ (± 0.341) (± 0.067)	6	0.969	0.153	23.8	(13)

was found. The calcd optimum π value is 1.91 (±0.234). For the set as a whole, eq 14 was calcd.

	n	*r*	*s*	*F*	
log potency = $0.480 + 1.106\pi - 0.251\pi^2$ (± 0.403) (± 0.077)	13	0.792	0.237	8.42	(14)

Although the *r* value is low both terms are significant at the 95% confidence level. The optimum π value is 2.11 (±0.491).

TABLE VII

In Vivo POTENCY OF CLINDAMYCIN ANALOGS

R	R′	Potency in mouse protection test Obsd[a]	Calcd[b]	Calcd[c]
H	C_2H_5	1.40	1.33	1.44
H	*n*-C_3H_7	1.93	1.57	1.77
H	*n*-C_4H_9	1.73	1.69	1.90
H	*n*-C_5H_{11}	1.83	1.68	1.86
H	*n*-C_6H_{13}	1.74	1.54	1.64
H	*n*-C_8H_{17}	0.61	0.89	0.64
CH_3	C_2H_5	1.15	1.57	
CH_3	C_3H_7	1.63	1.69	
CH_3	C_4H_9	1.50	1.68	
CH_3	C_5H_{11}	1.61	1.54	
C_2H_5	C_3H_7	1.50	1.68	
C_2H_5	C_4H_9	1.52	1.54	
C_2H_5	C_6H_{13}	1.10	0.89	

[a] Ref 2, 3. [b] Eq 14. [c] Eq 13.

Discussion

The results presented in this work support the previous observations of Lien, *et al.*,[11] and Hansch, *et al.*,[12] that the antimicrobial properties of many molecules are a function of the lipophilic nature of the molecule. In the first study the drugs were nonspecific toxic agents such as alcohols, amines, detergents, etc. They found an optimum log *P* for such compounds against Gram-positive organisms to be approximately 6. In the latter study[12] it was reported that for chloramphenicol analogs studied as inhibitors of *Escherichia coli* the optimum log *P* is 3.7. Both of these values are several log units higher than that calcd from these studies for lincomycin. These results suggest that it is not always possible to predict the optimum log *P* value for one series of compounds from the results of another series. Again, the lack of agreement between lincomycin and leucomycin supports this view.

The fact that both the lincomycin and clindamycin analogs show apparent optima for *in vivo* activity at a π value of approximately 2 is interesting. One would expect that a lincomycin would have a different log *P* value than the corresponding clindamycin. Thus these results suggest that the relative potency of members of these two sets of compounds depends only on the lipophilic nature of the pyrrolidine ring, and not that of the molecule as a whole.

Electronic effects could give at least a partial explanation for the fact that the lincomycins with the unsubstituted amino group yield what may be a higher optimum log *P*. The pK_a and σ^* values of the pyrrolidine ring and *N*-methylpyrrolidine ring have been determined by Hall.[13] Pyrrolidine has a pK_a of 11.27 and σ^* of −0.23 and its *N*-Me derivative has values of 10.46 and +0.26, respectively. This is a difference of 0.81 in pK_a and 0.49 in σ^*. Methylamine and NH_3 have the same differences. Assuming that such differences also apply approximately to lincomycin derivatives, the pK_a change would reflect differences in electron density at the nitrogen of this ring and could also lower the apparent partition coefficient of these compounds at any given pH. Since $EtNH_2$ differs from $MeNH_2$ by a

(11) E. J. Lien, C. Hansch, and S. M. Anderson, *J. Med. Chem.*, **11**, 430 (1968).
(12) C. Hansch, E. Kutter, and A. Leo, *ibid.*, **12**, 746 (1969).
(13) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1967).

ΔpK_a of 0.01 and $\Delta\sigma^*$ of 0.10, Et and Me derivatives should have similar optimum partition coefficients. The data in this report substantiate this observation.

This study demonstrates the usefulness of the extrathermodynamic approach in understanding structure–activity relationships. Thus, the antibacterial activities of leucomycins, as well as lincomycin and clindamycin analogs depend on their relative hydrophobic properties. Through use of dummy variables, steric effects could be examined in the lincomycin series. Finally, a comparison of the optimum π value for one subseries with that of another subseries results in the indication of an electronic effect. In the case of the leucomycin series the electronic and steric effects could not be separated because of lack of variety in the derivatives tested.

Antimalarial Agents. 8. Ring-Substituted Bis(4-aminophenyl) Sulfones and Their Precursors[1]

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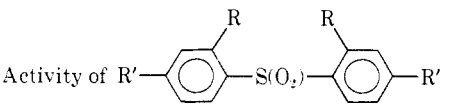
Forty-four compounds related to bis(4-aminophenyl) sulfone (DDS) were tested against *Plasmodium berghei* in mice. Seven of them were better antimalarial agents than DDS or equal to bis(4-acetamidophenyl) sulfone (DADDS). Ortho substitution to the NH_2 group of DDS resulted in total loss of activity. Meta substitution or N-acetylation did not lead to any general trend.

The acetylation of bis(4-aminophenyl) sulfone (I, 4,4′-diaminodiphenyl sulfone, DDS) to bis(4-acetamidophenyl) sulfone (II, *N*,*N*′-diacetyl-DDS, DADDS) resulted in a considerable improvement of activity against *Plasmodium berghei* in mice.[2,3]

Attempts for additional significant improvements of the antimalarial activity of DDS-related structures by replacing one or both NH_2 functions of DDS with various other groups have not been successful.[1a,3-6] The effect of ring substitution of I is described in this paper. Monosubstitution in the ortho or meta position to one of the NH_2 groups was expected to alter the nucleophilicity primarily of that group, to distort the apparent symmetry of the DDS-molecule, and to change its polarity. Meta mono- and meta,meta′ disubstitution (again relative to NH_2) should alter the shape of the molecule by H bonding or by steric or electromeric interactions of the substituent(s) with the adjacent SO_2 group much more than ortho substitution. Ortho substituents, however, could have a steric effect on the adjacent NH_2 group. Finally, symmetrical substitution in both Ph rings should render both amino moieties equally different from the NH_2 groups of DDS. The activity data obtained by a previously published method[7] and listed in Tables I–IV were evaluated in view of the expected changes of the DDS molecule brought about by the ring substituents CH_3, CF_3, CO_2Me, NH_2, NHAc, NO_2, OMe, and Cl.

TABLE I

Activity of 

Compound No.	Structure R	Structure R′	CIST[f] or (% cures) at mg/kg 40	160	640
I[a]	H	NH_2	8.0	(40)	(20)[g]
II[a]	H	NHAc	(20)	(100)	(100)
III[b]	NH_2	NH_2	8.8	(40)	(100)
IV	NHC(O)H	NHC(O)H	0.9	4.9	12.3
V[c]	Cl	NO_2	0.7	3.5	13.9
VI[c]	Cl	NH_2	4.7	(40)	(60)
VII[d]	Me	NH_2	1.5	9.9	(60)[h]
VIII	CO_2Me	NO_2	0.3	0.3	0.5
IX	CO_2Me	NH_2	0.2	0.6	0.8
X	CO_2Me	NHAc	0.9	0.9	1.1
XI[e]	CF_3	NO_2	0	0	0.2
XII[e]	CF_3	NH_2	0.2	0.2	0.4

[a] Test data supplied by Dr. B. Poon of Walter Reed Army Institute for Research. [b] H. Bradburry and F. J. Smith, *J. Chem. Soc.*, 793 (1956). [c] S. S. Berg, *ibid.*, 1991 (1949). [d] M. Balasubramanian and V. Baliah, *ibid.*, 1251 (1955). [e] G. W. Stacy, C. R. Bresson, R. E. Harmon, and R. C. Thamm, *J. Org. Chem.*, **22**, 298 (1957). [f] Change in survival time, *i.e.*, mean survival time of treated mice minus the mean survival time of the control. [g] 80% toxic deaths at 640 mg/kg. [h] 40% toxic deaths at 640 mg/kg.

Ortho mono- and ortho,ortho′ disubstitutions of I resulted in a general trend, *i.e.*, they rendered the DDS structure inactive (XXXII–XXXV, XL, XLIII, and XLVI). Since both electron-withdrawing and -donating substituents had the same effect, it appears that internal H bonding or distortion of a favorable spacial NH_2 arrangement of DDS caused the deactivation. The significance of the position of a substituent is well illustrated by the test data for CF_3-substituted structures XXIII and XLIII. Meta mono- and meta,meta′ disubstitutions, however, did not lead to any general conclusion on the antiplasmodial activity effect of substituents and did not indicate any structure–activity

† In memory of my teacher, Professor Clemens Schöpf, deceased December 17, 1970.

(1) (a) Part 7: *J. Med. Chem.*, **14**, 550 (1971); (b) this study was supported by U. S. Army Medical Research and Development Command; This is Contribution No. 948, from the Army Research Program on Malaria. (c) the compounds were tested by Dr. L. Rane of the University of Miami, Florida; (d) analyses are indicated by symbols of the elements, since analytical results obtained for these elements were within ±0.4% of the theoretical values.

(2) Test data supplied by Dr. Bing Poon of Walter Reed Army Institute for Research.

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