three neurotoxins were isolated from unialgal cultures of the dinoflagellate *G. breve* Davis (the red-tide organism). Of the three toxins as assayed in mice, only one (T_1) has hemolytic activity. None of the toxins possesses antiacetylcholinesterase activity. The major toxin (T_2) appears to have a molecular weight of 725. This toxin is unsaturated and has no hydroxy groups, but it possesses a nitrogen (Dragendorff positive). The toxin has at least two oxygens in a lactone ring or in an ester bond. The physicochemical and toxicological properties of the toxin T_2 were contrasted with toxins isolated by other workers. Ciguatoxin may be a metabolic product of the major toxin T_2 or a closely related substance from blue-green algae.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 13, 1974, from the **Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, TX 77550,* the *‡Department of Marine Sciences, Moody College of Marine Sciences and Maritime Resources, Texas A & M University, Galveston, TX 77550,* and the *§Department of Chemistry, Rice University, Houston, TX 77004*

Accepted for publication October 11, 1974.

Supported by Grant H-416 from the Robert A. Welch Foundation, Houston, Tex., and Food and Drug Administration Grant FD-00151-08.

The authors thank Mrs. Anita Aldrich for culturing and ether extraction of the cell culture.

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Determination of Sigma and Pi Constants of Quinolinium Acid Derivatives

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Abstract □ The apparent partition coefficients of 10 quinoline monocarboxylic acid derivatives in a chloroform–water system were determined. From these data, Hammett's σ and Hansch's π values were calculated.

Keyphrases □ Quinolinium acid derivatives—partition coefficients in chloroform–water system, sigma and pi constants □ Partition coefficients—10 quinoline monocarboxylic acid derivatives in chloroform–water system, sigma and pi constants □ Sigma constants—quinolinium acid derivatives □ Pi constants—quinolinium acid derivatives

By using Hammett's (1) equation (Eq. 1), considerable information concerning the effects of substituents on the reaction of given groups in the benzene series is available:

$$\log k - \log k_0 = \sigma\rho \qquad \text{(Eq. 1)}$$

where k is the rate or equilibrium constant for reactions of the substituents, k_0 is the corresponding rate or equilibrium constant of the unsubstituted compound, σ measures a change in electron density produced by a substituent, and ρ measures the susceptibility of the reaction in question to changes in electron density. The application of the Hammett equation has been relatively limited in heterocyclic compounds due to the presence of heteroatoms which themselves are capable of producing changes in electron density (2–8).

Furthermore, Hansch defined π as:

$$\pi = \log P_x - \log P_H \qquad \text{(Eq. 2)}$$

where P_H is the partition coefficient of a parent compound, and P_x is the partition coefficient of a derivative. It was shown by Hansch *et al.* (9–11) that a substituent constant, π, patterned after the Hammett σ constant, was useful in evaluating the lipohydrophilic character of a molecule upon which biological activity is dependent.

Table I—pK_{app} Values of the Sodium Alkyl Sulfates of Some Esters of *N*-Methylquinolinium Acids

N-Methyliodides of	pK_{app} of Alkyl Sulfates				
	C_9	C_{10}	C_{11}	C_{12}	ΔC
Quinoline	2.79	3.24	3.78	4.20	3.5
2-Ethyl ester quinoline carboxylic acid	3.62	4.08	4.56	5.03	4.33
3-Ethyl ester quinoline carboxylic acid	3.41	3.89	4.90	4.76	4.10
4-Ethyl ester quinoline carboxylic acid	4.26	4.72	5.18	5.63	4.95
5-Ethyl ester quinoline carboxylic acid	3.87	4.39	4.97	5.57	4.70
6-Ethyl ester quinoline carboxylic acid	3.55	3.98	4.40	4.84	4.19
6-Methyl ester quinoline carboxylic acid	3.48	3.93	4.35	4.80	4.14
6-Propyl ester quinoline carboxylic acid	3.74	4.26	4.76	5.24	4.50
6-Butyl ester quinoline carboxylic acid	4.29	4.74	5.26	5.76	5.01
3-Propyl ester quinoline carboxylic acid	3.41	3.95	4.46	4.97	4.20
3-Acetamido ester quinoline carboxylic acid	3.95	4.38	4.83	5.30	4.61

The present investigation was confined to the determination of the apparent partition coefficients of the quinolinium acid derivatives and the calculation of the Hammett σ and Hansch π constants.

EXPERIMENTAL

Materials—The following were used: 2-ethyl-, 3-ethyl-, 4-ethyl-, 5-ethyl-, 6-ethyl-, 3-propyl-, 6-propyl-, 6-methyl-, and 6-butylquinolinic acids[1]; 3-acetamidoquinoline[1]; methyl iodide[1]; and chloroform[2].

Synthesis—The sodium alkyl sulfates were synthesized as previously described (12, 13). The syntheses of quinolinium acid derivatives are reported elsewhere (14).

Determination of Apparent Partition Coefficient (K_{app})—The K_{app}'s were determined by previously published methods (13, 15–17). That is, initial studies had indicated that the alkyl sulfates–*N*-methylquinolinium derivative salts exist as ion-ion-pair monomers in the organic phase. Therefore, a log–log plot of the concentration of ions in the chloroform phase would yield a slope of 2 with the *Y* intercept being equal to pK_{app} according to Eq. 3:

$$pK_{app} + 2 \log \text{concen}_{aq} = \log \text{concen}_{CHCl_3} \quad \text{(Eq. 3)}$$

By using Eq. 3, the pK_{app} values of the various alkyl sulfates of the quaternary derivatives of the quinolinic acids were calculated (Table I). The wavelength of the maximum absorbance and the molar absorptivity for these compounds are listed in Table II.

RESULTS AND DISCUSSION

The structures of the compounds listed in Table I were correlated by using the Hammett equation (Eq. 1).

The pK_{app} for the *N*-methylquinolinium alkyl sulfate was chosen to be k_0, and the pK_{app} for each *N*-methylquinolinium acid ester alkyl sulfate derivative was considered to be k. The ρ value of 2.113, as reported by Albert and Phillips (18), was used. By using the pK_{app} values reported in Table I, the Hammett function, σ, was calculated for each compound. Good agreement was achieved as illustrated in Fig. 1. Quinoline-5- and 6-carboxylic acids esters may be regarded as substituted benzoic acids in which the fused pyridine ring is considered as a substituent. In the quinoline-2-, 3-, and 4-carboxylic acid esters, the fused benzene ring may be considered as one substituent, and the electron-attracting ring nitrogen may be considered the second substituent.

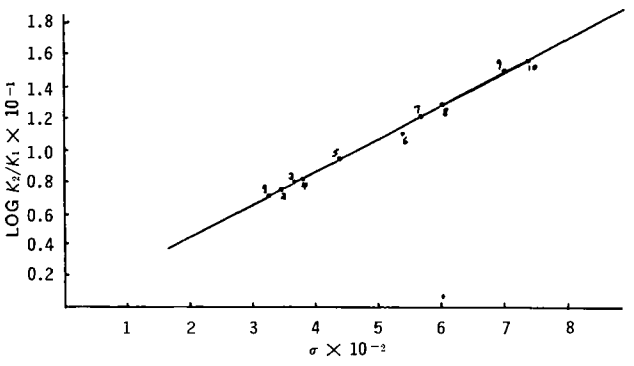

Figure 1—*Relationship between log* K_2/K_1 *and* σ *for various quinolinium acid derivatives. Key: 1, 3-*$COOC_2H_5$*; 2, 6-*$COOCH_3$*; 3, 6-*$COOC_2H_5$*; 4, 3-*$COOC_2H_5$*; 5, 2-*$COOC_2H_5$*; 6, 6-*$COOC_3H_7$*; 7, 3-*$CONH_2$*; 8, 5-*$COOC_2H_5$*; 9, 4-*$COOC_2H_5$*; and 10, 6-*$COOC_2H_5$.

Hammett (1) showed that a linear relationship exists between equilibrium and rate constants for practically all side-chain reactions of benzene derivatives containing *meta*- or *para*-substituents. Furthermore, a condition for such a linear relationship is that there be no significant change in entropy of activation. However, despite these assumptions, it is interesting that such a linear relationship exists (Fig. 1).

Hansch and Fujita (11) used partition coefficients in connection with the Hammett equation to rationalize the substituent effect on the growth-promoting activity of the phenoxyacetic acids and the bactericidal action of chloramphenicol derivatives on various bacteria. They showed that a substituent constant, π, patterned after

Table II—Wavelength of Maximum Absorbance and Molar Absorptivity of Some Esters of *N*-Methylquinolinium Acids

N-Methyliodides of	λ_{max}	Molar Absorptivity, $\times 10^3$
Quinoline	235	4.25
2-Ethyl ester quinoline carboxylic acid	248	2.60
3-Ethyl ester quinoline carboxylic acid	235	5.60
4-Ethyl ester quinoline carboxylic acid	237	2.70
5-Ethyl ester quinoline carboxylic acid	232	4.66
6-Ethyl ester quinoline carboxylic acid	245	3.70
6-Methyl ester quinoline carboxylic acid	242	5.75
6-Propyl ester quinoline carboxylic acid	246	3.50
6-Butyl ester quinoline carboxylic acid	246	3.10
3-Propyl ester quinoline carboxylic acid	246	3.08
3-Acetamido ester quinoline carboxylic acid	238	4.25

Table III—Hansch π Values of Some Esters of *N*-Methylquinolinium Acids

N-Methylquinolinium of	π Constant
2-Ethyl ester quinoline carboxylic acid	0.09
3-Ethyl ester qunoline carboxylic acid	0.07
4-Ethyl ester quinoline carboxylic acid	0.15
5-Ethyl ester quinoline carboxylic acid	0.13
6-Ethyl ester quinoline carboxylic acid	0.08
6-Methyl ester quinoline carboxylic acid	0.08
6-Propyl ester quinoline carboxylic acid	0.11
6-Butyl ester quinoline carboxylic acid	0.16
3-Propyl ester quinoline carboxylic acid	0.08
3-Acetamido ester quinoline carboxylic acid	0.12

[1] K & K Laboratories.
[2] Matheson, Coleman and Bell.

Table IV—pK_{app} Values per Carbon Atom in Alkyl Sulfates of Some Esters of *N*-Methylquinolinium Acids

N-Methyliodides of	pK_{app} per Carbon Atom in Alkyl Sulfates
2-Ethyl ester quinoline carboxylic acid	0.47
3-Ethyl ester quinoline carboxylic acid	0.45
4-Ethyl ester quinoline carboxylic acid	0.46
5-Ethyl ester quinoline carboxylic acid	0.57
6-Ethyl ester quinoline carboxylic acid	0.43
6-Methyl ester quinoline carboxylic acid	0.44
6-Propyl ester quinoline carboxylic acid	0.50
6-Butyl ester quinoline carboxylic acid	0.50
3-Propyl ester quinoline carboxylic acid	0.52
3-Acetamido ester quinoline carboxylic acid	0.45

the Hammett σ constant, was useful in evaluating the lipohydrophilic character of a molecule upon which biological activity is dependent (Eq. 2).

By using the quinolinium methyliodide as P_H and the different esters of quinolinium acids as P_x, values for π were calculated (Table III).

The change in pK_{app} per carbon atom in the alkyl sulfates of the esters of the quinolinium acid derivatives was found to have an average value of 0.48 (range 0.43–0.57) (Table IV), which is in reasonable agreement with the value of 0.44 for each CH_2 unit reported by Hansch *et al.* (11) and with the value of 0.46 reported by Plakogiannis (7).

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ACKNOWLEDGMENTS AND ADDRESSES

Received September 5, 1974, from the *Brooklyn College of Pharmacy, Long Island University, Brooklyn, NY 11216*

Accepted for publication October 17, 1974.

Presented at the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, April 1975.

The author is a recipient of a Lederle Pharmacy Faculty Award for 1975.

Oral Absorption Efficiency of Acid-Labile Antibiotics from Lipid–Drug Delivery Systems

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Abstract □ The utility of cholesterol, cholesteryl acetate, and β-sitosterol in protecting and improving the oral absorption efficiency of acid-labile antibiotics is discussed. The potassium salts of penicillin G and penicillin V and erythromycin lactobionate were studied. The stability of the two penicillins in simulated gastric fluid was determined iodometrically. The rank order of acid protective activity was: cholesteryl acetate > β-sitosterol > cholesterol. Oral administration of erythromycin lactobionate coated with cholesteryl acetate produced a twofold increase in human urinary excretion of erythromycin when compared with the uncoated material. Potassium salts of penicillin G and penicillin V coated with cholesteryl acetate yielded 1.6- and 2-fold higher urine levels, respectively, as compared with the uncoated candidates.

Keyphrases □ Antibiotics, acid labile—oral absorption efficiency of penicillin G potassium, penicillin V potassium, and erythromycin lactobionate from cholesterol, cholesteryl acetate, and β-sitosterol protective carriers □ Penicillins G and V (potassium)—oral absorption efficiency from lipid–drug delivery systems □ Erythromycin lactobionate—oral absorption efficiency from lipid–drug delivery systems □ Lipid–drug delivery systems—oral absorption efficiency of penicillin G potassium, penicillin V potassium, and erythromycin lactobionate from cholesterol, cholesteryl acetate, and β-sitosterol protective carriers.

Solutions of penicillin G lose 50% of their potency in less than 1 min at pH 1 and in about 9 min at pH 2 (1). Solutions of penicillin V in 0.1 *N* hydrochloric acid at 37° were reported to have a half-life of 29 min (2). Chemical inactivation of penicillin G in the gastric fluid has been reported to be responsible for the