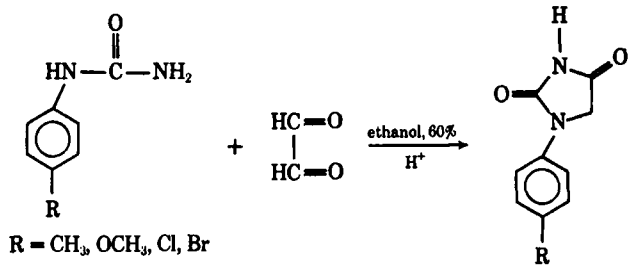

Scheme I

the nature or the yield of the reaction products is not influenced significantly by either factor.

EXPERIMENTAL[3]

The preparation of compounds listed in Table I is exemplified by the following method described for 1-*p*-methylphenylhydantoin (I).

To a hot solution of 3.0 g. (0.02 mole) of *p*-tolylurea in 50 ml. of 50% ethanol was added 1.56 g. (0.02 mole) of 80% glyoxal, followed by 10 ml. of a 10% solution of hydrochloric acid in ethanol. The solution was heated under reflux for 6–10 hr. A solid that formed was separated from the hot reaction medium to give 1.05 g. of first crop, whose NMR spectrum indicated that it was a mixture of I containing less than 5% 1,4-di-*p*-tolyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione. Crystallization of this crop from methanol gave 0.9 g. of pure I. The filtrate from the reaction mixture was allowed to remain at room temperature for about 2 hr., at which time an additional 0.4 g. of solid was separated. This crop was identified to be I. A third crop, 0.5 g., obtained after complete evaporation of filtrate, contained about 10% of the 3-substituted isomer of I. Crystallization of this crop from methanol gave 0.3 g. of pure I. The combined yield of I was 1.6 g. (43%), m.p. 212–214°. Microanalysis is recorded in Table I.

[3] Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were determined on a Perkin-Elmer R-12. Sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used as a reference; trifluoroacetic acid was used as a solvent except for Compound II for which dimethyl sulfoxide was used. The IR spectra were determined in KBr disk with a Beckman IR-8 instrument.

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COMMUNICATIONS

Effect of Chain Length in Homologous Series of Anionic Surfactants on Irritant Action and Toxicity

Keyphrases □ Chain length effect—irritant action and toxicity of homologous series of anionic surfactants □ Surfactants, anionic—effect of chain length in homologous series on irritant action and toxicity □ Toxicity, anionic surfactants—effect of chain length in homologous series □ Irritant action, anionic surfactants—effect of chain length in homologous series □ Skin—effect of chain length of anionic surfactants on swelling and irritant action

Sir:

Among the investigations into the irritant action and toxicity of homologous series of anionic surfactants containing a single normal alkyl chain are the following. Choman investigated the swelling of human skin in solutions of sodium alkyl sulfates (1) and the swelling of dermal collagen of calf in sodium soaps (2). Edwards (3) studied the effect of sodium soaps on the lysis of red blood cells and on segments of earthworms, while Emery and Edwards (4) studied their irritant action on human skin. Gale and Scott (5) investigated the intraperitoneal and oral toxicity of sodium alkyl sulfates as well as their effects on various types of muscles. In these and other investigations, the greatest effects among the sodium alkyl sulfates ranging from octyl to octadecyl were shown by the dodecyl sulfate. In the series of soaps ranging from sodium octanoate to stearate, sodium laurate displayed the highest activity. Representative curves are shown in Figs. 1 and 2. Figure 1 refers to the net swelling, *i.e.*, swelling in the surfactant solutions minus swelling in pure water, measured as increase in thickness. The surfactant solutions were at or slightly above the CMC.

The purpose of this communication is to present a hypothesis to explain the maximum effectiveness observed for intermediate members of the homologous series. Maxima or minima in the relationship between two variables often arise from the effect of two opposing factors on these variables, one of which tends to enhance the relationship while the other tends to diminish it. In the present case, one of the two factors affecting the relationship between the length of the alkyl chain of

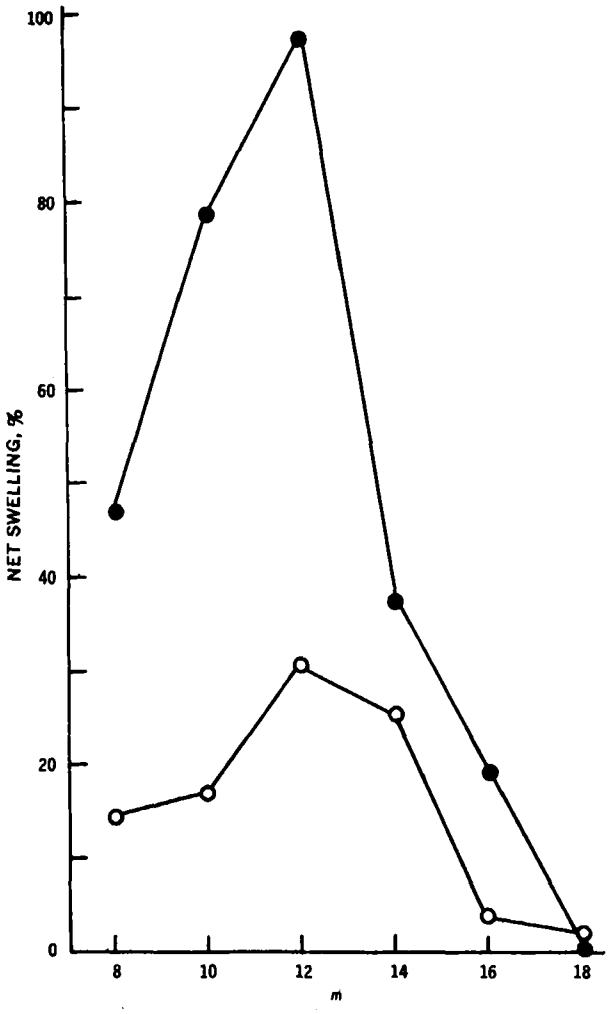

Figure 1—*Net swelling of calf skin collagen in sodium soap solutions and of human skin in sodium alkyl sulfate solutions as a function of the number,* m, *of carbon atoms per surfactant molecule. Key:* ○, *human skin in sodium alkyl sulfate solutions (from data of* Reference 1*);* ***and*** ●, *calf skin collagen in sodium soap solutions (from data of* Reference 2*).*

anionic surfactants and their interaction with proteins is the oil–water partition coefficient P. The other factor is the upper limit of the concentration of nonassociated surfactant molecules attainable in the aqueous phase, given by the surfactant solubility below the Krafft point and by the CMC above it.

Oil–Water Partition Coefficients—Partition coefficients of ionic surfactants between octanol and water increase monotonically within a given homologous series. Augmenting the chain length by an ethylene group increased log P by about 0.8 (6). According to:

$$\Delta G = -RT \ln P \qquad \text{(Eq. 1)}$$

the free energy of transfer of an ethylene group from water to octanol at room temperature is −1090 cal./mole. This estimate assumes that the ionic surfactants are equally ionized in water and in octanol. Despite the fact that the water concentration in octanol saturated with water is 2.3 M (more than 25 mole-%) (6), which should lead to considerable ionization of the surfactant molecules in the oil phase, the true P values are probably lower than the apparent partition coefficients obtained from analytical data. Nevertheless, the ΔG value is in reasonable agreement with the value of −1280 cal./mole corresponding to the transfer of an ethylene group from water to the hydrocarbon interior of a micelle (7). Part of the difference is probably due to the fact that the transition from water to octanol saturated with water is less abrupt than that from water to a liquid paraffinic hydrocarbon. Similarly, it is seen from Table I that the CMC decreases approximately by a factor of 4 in a homologous series for each increase in the chain length by an ethylene group; log 4 = 0.6 is reasonably close to the corresponding increase of 0.8 in log P.

According to the hypothesis of this communication, the increase in the oil–water partition coefficient with increasing chain length n is responsible for the ascending branches of the curves in Figs. 1 and 2. In the physiological situations, the oil phase in contact with the aqueous surfactant solutions consists of collagen, skin, muscle tissue, erythrocyte membrane, *etc.*

Limiting Monomer Activity—In all likelihood, only monomeric or nonmicellar surfactant molecules enter the "oil" (collagen, skin, or muscle tissue) phase or interact with erythrocyte membranes. The upper limit

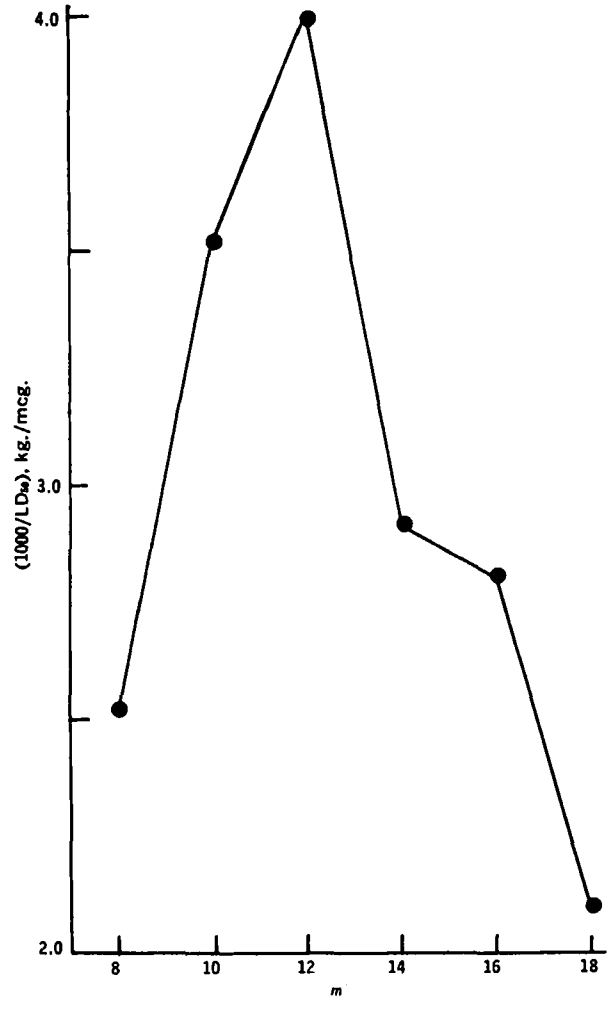

Figure 2—*Reciprocal of intraperitoneal* LD_{50} *values of sodium alkyl sulfates for mice* versus *the number,* m, *of carbon atoms per surfactant molecule (from data of* Reference 5*).*

Table I—Values of Krafft Point and CMC for Sodium Soaps and Sodium Alkyl Sulfates in Water

n^a	Krafft Point[b]	CMC[c], moles/l. × 10^3
	$C_nH_{2n+1}OSO_3Na$	
10	8°	33.1 (25°)
12	20°	8.1 (25°)
14	33°	2.2 (40°)
16	46°	0.5 (40°)
18	58°	—
	$C_nH_{2n+1}COONa$	
7	—	340 (25°)
9	—	94 (25°)
11	36°	24.4 (25°)
13	53°	7.1 (50°)
15	62°	—
17	71°	—

[a] Number of carbon atoms in the normal alkyl chain. [b] From *Reference 8.* [c] From *Reference 9.*

for the concentration of nonassociated surfactant molecules is the solubility limit at temperatures below the Krafft point and the CMC above it. The solubility at the Krafft point is equal to the CMC (7). The monomer activity of aqueous surfactant solutions increases only slightly after the overall concentration has been raised above the CMC because the bulk of the surfactant added in excess of the CMC forms micelles. CMC values and Krafft points for two homologous series of anionic surfactants are assembled in Table I.

As the alkyl chain length increases on ascending a homologous series, there is a monotonic decrease in the maximum concentration of single or nonmicellar surfactant species owing to a decrease in solubility or in the CMC. This effect is responsible for the downturn in the curves of Figs. 1 and 2. This reasoning is only valid if, at temperatures above the Krafft point, the surfactant concentrations in the aqueous phase are equal to or exceed the CMC values.

Conclusion—With the oil–water partition coefficient increasing and the limiting monomer concentration decreasing on ascending a homologous series, a maximum surfactant concentration in the "oil" (collagen, skin, muscle tissue, or erythrocyte membrane) phase is found at an intermediate chain length. As a result, a surfactant of intermediate chain length has the greatest irritant, toxic, or hemolytic effectiveness.

It is to be expected that the chain length for maximum effectiveness within each homologous series depends on the hydrophilicity of the polar headgroup, being greater for the more hydrophilic groups. The $—O—SO_3^-\ Na^+$ group is more hydrophilic than the $—COO^-\ Na^+$ group. The most active alkyl sulfate was found to be the dodecyl ester ($m = n = 12$), whereas sodium laurate ($m = 12$ but $n = 11$) was the most active soap. Unfortunately, only surfactants with even numbers m of carbon atoms were investigated in the two homologous series, making the most effective member among the alkyl sulfates the one with $n = 12 \pm 1$ and among the soaps the one with $n = 11 \pm 1$; n is the number of carbon atoms in the alkyl chain.

Since the increase in P and the decrease in the CMC as a function of n are of comparable magnitude, the ascending and descending branches of curves like the ones of Figs. 1 and 2 should have slopes of comparable absolute values though of opposite signs, as long as the experimental temperatures exceed the Krafft points.

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Enhancement of Intestinal Absorption of a Quaternary Ammonium Compound by Salicylate and Trichloroacetate

Keyphrases ☐ Quaternary ammonium compounds—enhancement of intestinal absorption by salicylate and trichloroacetate ☐ Ammonium compounds, quaternary—enhancement of intestinal absorption by salicylate and trichloroacetate ☐ Absorption, intestinal—effect of salicylate and trichloroacetate on *N,N*-bis(phenylcarbamoylmethyl)dimethylammonium chloride absorption ☐ Salicylate effect—intestinal absorption of a quaternary ammonium compound ☐ Trichloroacetate effect—intestinal absorption of a quaternary ammonium compound

Sir:

The possibility of increasing the GI absorption of poorly permeable, charged drug molecules by formation of lipoid-soluble ion-pairs with various counterions has received a good deal of attention (1–7). The present report concerns the influence of certain anions on the intestinal absorption of *N,N*-bis(phenylcarbamoylmethyl)dimethylammonium chloride (I), a quaternary ammonium compound with antiarrythmic activity[1].

The purity of the drug[2], tritium-labeled on an *N*-methyl group (specific activity 14.5 μc./mg.) as well as

[1] Personal communication, Astra Pharmaceutical Products, Inc., Worcester, Mass.
[2] Provided by Astra Pharmaceutical Products, Inc.