THE RELATION BETWEEN STRUCTURE AND PHYSIOLOGICAL ACTION OF THE ALCOHOLS.*

BY OLIVER KAMM.

The reaction of the living organism towards chemical reagents is usually of a character sufficiently complex to discourage attempts at generalization. It was because of this reason that the present inquiry into the relationship between physiological action and chemical constitution was limited to an extremely simple class of organic compounds, the mono-hydroxy primary aliphatic alcohols, it being the intention to carry the study progressively to the less common members as well as to aromatic derivatives of the benzyl type.

Although this initial study was considerably and intentionally restricted from the chemical side, the physiological effect studied (toxicity) was directed toward various types of organisms. An attempt has been made also to seek the relation between certain physical and chemical properties of these alcohols and their relative toxic action. The data utilized in the subsequent discussion has been drawn not only from the writer's own observations but also from data previously published.

Morgan and Cooper[1] have studied the effect of chemical constitution upon the germicidal power of the mono-hydroxy aliphatic alcohols and have presented data to show that the toxicity in a given homologous series increases in the order of the molecular weights. The same generalization has been completely verified by Macht[2] in a study of the acute toxicity of these alcohols when injected into the blood stream of the cat. This generalization, known as Richardson's Rule, has been the subject of numerous investigations, references to which may be found in Macht's recent contribution to the subject.

It is the purpose of this report to connect Macht's toxicological data and that already available from the bacteriological standpoint, with additional observations made by the writer, in two directions, viz.: (a) the effect of alcohols on the coagulation of proteins, and (b) the toxicity of alcohols to paramecia.

A comparison between these values, obtained from such varied sources, is well illustrated in the following table in which the effect of ethyl alcohol is expressed as unity:

Alcohol used.	Acute toxicity to cats (Macht).	Germicidal powers (Morgan & Cooper).	Toxicity to paramecia (Kamm).	Albumen coagulating power (Kamm).
Methyl	0.8	0.95	0.8	0.9
Ethyl	1.0	1.0	1.0	1.0
n-Propyl	2.5	2.5	1.9	2.0
n-Butyl	16.6	8.0	4.5	5.0

In testing the albumen coagulating powers of the alcohols a 5 percent solution of egg albumen was used and comparative observations made at a temperature of 50° C. The concentration of alcohol necessary to produce practically complete coagulation during 10–15 minutes was then determined. The results

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[1] Eighth Int. Cong. Appl. Chem., VIII, d, p. 245 (1912).

[2] *J. Pharmacol.*, 16, 1 (1920).

are expressed in terms of ethyl alcohol as unity, methyl alcohol being found slightly less efficient than ethyl alcohol, whereas 2 percent *n*-butyl alcohol produced an effect equal to a 10 percent concentration of ethyl alcohol. These results are of only a preliminary character.

The data for toxicity to paramecia presented above are found to obey the rule that in this series of alcohols the physiological action increases with increasing molecular weight, and this generalization holds also for the protein-coagulating powers of these alcohols.

Since the physical properties of these alcohols also vary progressively with the molecular weights we must conclude that the effects upon the living organism present no special abnormality and it would appear that one may now predict the toxicity of compounds in this series with approximately the facility with which the chemist has been accustomed to predict their physical properties. Where abnormal physical and chemical properties occur one meets corresponding abnormal physiological effects.

The values for methyl alcohol as given in the above table possess little relation to the deleterious action of methyl alcohol when taken into the digestive tract. It has been repeatedly pointed out by many writers that the latter action is due to secondary effects called forth possibly by the intermediate oxidation products of methyl alcohol, and these secondary effects are not directly connected with the above measurements of acute toxicity.

The high antiseptic power of normal butyl alcohol, which possesses a phenol coefficient of 0.25, is of interest because of the availability of this compound. Before the war this material was classified as a rather rare chemical and many of its simple derivatives were unknown. During the war, however, this alcohol was obtained as a by-product in the production of acetone by fermentation of carbohydrate material, and it is now one of the cheapest of organic chemicals.

In seeking a numerical expression for the above results the writer was surprised to note the semi-quantitative agreement with the following geometrical progression:

$$1 : 3^1 : 3^2 : 3^3,$$

provided that the values for the alcohols be expressed as moles and not as grammes, ethyl alcohol being represented as the first member. Thus for protein coagulation the observed values are:

$$\text{Ethyl} : \text{Propyl} : \text{Butyl}$$
$$1.0 \quad : \quad 2.6 \quad : \quad 8.0$$

Reference to the first table shows that the toxicity values on paramecia (when reinterpreted in moles) are not far removed from this generalization. Normal propyl alcohol agrees well with this rule even in its toxicity towards cats, but abnormalities are met with in butyl alcohol which may possibly be ascribed to the fact that a too concentrated solution of this effective material was injected intravenously. The concentration used by Macht (5 percent) is extremely effective in coagulating protein and it would therefore be of interest to determine toxicity using a 1 percent solution.

Upon first consideration it might appear as if protein coagulation were the prime cause of toxicity in all of these tests. It is not intended, however, to convey

this impression. A second important factor to be considered is the increase of toxicity due to increase in lipoid solubility as one goes higher in this homologous series. Toxicity when the material is injected into the blood stream is no doubt greatly dependent upon the latter factor, which here may become more important than the protein coagulating factor. Macht has presented data for the iso-alcohols (isopropyl, isobutyl, and isoamyl) in respect to toxicity when injected into the blood stream, the relative toxicities observed being $1 : 2.75 : 9.6$ which yield the ratios $1 : 3.4 : 14$ when expressed as moles.

A natural question that now arises is this: To what extent will this semi-quantitative generalization hold among the higher homologues? This is to be answered experimentally, although one may predict that the higher homologues which approach closer and closer to the hydrocarbons in their physical properties, will be so slightly soluble in water that they may not admit of being subjected to a legitimate test. This limit will no doubt be found between the range C_6-C_{10}.

The above "rule of three" is of interest especially because Traube[1] has shown that such a relation exists between the relative surface tensions of aqueous solutions of these alcohols, and, what is still more important, he has also shown that hypnotic action of certain classes of compounds, particularly the urethanes, obeys this same numerical rule.

Although within a given homologous series of alcohols both toxicity and hypnotic action increase regularly with increasing molecular weight, the opposite may be found true in comparing alcohols falling in different homologous series. Thus the normal primary, secondary, iso, and tertiary alcohols, respectively, *decrease* in toxicity as we go from the straight chain to the branched molecule. On the other hand, hypnotic action fortunately *increases* in the same order.

The present treatment of the subject, directed toward the simplest class of alcohols, and only to the lower members in this class, is intended simply as an elementary basis for later work.

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PHARMACEUTICAL RESEARCH.*

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The most ancient records available show that from time immemorial the progressive peoples of each period recognized that the preparation and dispensing of medicines was an important vocation to be entrusted only to those specially trained and educated to perform such duty to society. In ancient Egypt, the priests of Isis alone compounded and dispensed the prescriptions of the physician priests. The Israelites evidently held the apothecaries in high esteem as the Biblical records contain a number of references to them and their work. The holy anointing oil and the incense were both directed to be "compounded after the art of the apothecary." To Eleazar of the priesthood, the son of Aaron, were entrusted the services and duties at that time performed by the apothecary.

[1] Pflügers *Arch. Physiol.*, 105, 559.