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TEACHING THE MEANING OF CHEMICAL STRUCTURE.*

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A structural formula should reveal something about its chemical properties, physical properties and pharmacological action.

Organic Chemistry has been defined as "an edifice reared on structural formulas." We who are interested in the teaching of Organic Chemistry find this an apt definition if the meaning of structural chemistry and its limitation be clearly understood. There can hardly be a greater waste of mental energy than to memorize structural formulas without a full understanding of their meaning. The structural formula should not be taught as an end in itself but as a means to an end, a condensed way of setting down in a small space a vast amount of information.

The structural formula isn't taught until the *fundamental bases* underlying the Structural Theory of Organic Chemistry has been considered. At this stage the student knows how to determine the molecular formula. If we give the formula for ethyl alcohol as C_2H_6O the student knows how that formula is determined but if we write the structural formula $CH_3.CH_2OH$ he asks why not write the formula $CH_3.O.CH_3$. It is obvious to the student that there is a difference in these two formulas and that something more than valency must be considered to determine the correct formula. When this fact is recognized the student's question is answered by introducing the second step, in order to determine the correct formula, which is a study of chemical behavior. The following reaction will explain how the right formula is derived.

Upon treating ethyl alcohol with sodium there is a reaction which yields one atom of hydrogen for every atom of sodium per molecule of ethyl alcohol yielding a compound which has the molecular formula C_2H_5ONa. The other five atoms cannot be displaced no matter how much sodium is used. Again, when ethyl alcohol is treated with a binary halogen acid, *e. g.*, hydrochloric, under favorable conditions one atom of oxygen and one atom of hydrogen are displaced by one atom of chlorine, producing a compound that has the molecular formula C_2H_5Cl. When this compound is heated with water it is transformed into ethyl alcohol, one atom of chlorine being displaced by one atom of oxygen and a proportional quantity of hydrogen. From these two experiments and a number of others it is concluded that ethyl alcohol contains one atom of hydrogen combined differently from the other five, also that one atom of hydrogen must be closely associated with the oxygen atom forming a univalent radicle—OH; if this were not the case it would be difficult to understand how an atom of univalent chlorine could displace, or be displaced by, an atom of univalent hydrogen and an atom of bivalent oxygen.

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Further since the compound C_2H_5Cl does not contain a hydrogen atom that can be displaced by sodium it is concluded that the particular hydrogen atom in ethyl alcohol that is displaceable by sodium, is the same as that which is closely associated with the oxygen atom, hence the structure of the sodium derivative must be $CH_3.CH_2ONa$. Therefore the structure of ethyl alcohol based upon its chemical behavior and valency considerations must be $CH_3.CH_2.OH$.

It is thus possible with the help of valency considerations and the study of chemical behavior to determine the state of combination of all the atoms of which the molecule is composed and express the result in a structural formula.

Inversely, the structural formulas represent all the chemical properties of the compounds, and are simply a short way of expressing them. Thus compounds which are found to show a similar behavior are considered to contain atoms or groups of atoms in a similar state of combination.

In addition to these properties the structural formulas aided by a study of molecular weight give us a picture of their physical properties. Any class of compounds can be taken to illustrate this point but having started on the alcohols let us use them for further consideration. A few examples will explain this relationship.

The solubility in water decreases with increase in molecular weight. Compounds from CH_3OH to C_4H_9OH are limpid liquids, those from $C_5H_{11}OH$ to $C_{11}H_{23}OH$ are of oily consistency, and from $C_{12}H_{25}OH$ up they are solids. An increase in the number of OH groups tends to increase the degree of sweetness. Methanol CH_3OH is not sweet; glycol $C_2H_4(OH)_2$ is somewhat sweet; glycerol $C_3H_5(OH)$ is sweet; while mannitol $C_6H_6(OH)_6$ is still sweeter. The lower alcohols have characteristic odors while the higher alcohols are practically odorless.

Other very important lessons are written in a structural formula, but to a student interested in Pharmacy and Medicine probably the most important is to be able to read the relationship of chemical structure to pharmacological action and its relative degree of activity. For example, let us consider the following alcohols which have been tested pharmacologically by Overton on tadpoles and by Vernon on tortoises.

Methyl alcohol	CH_3OH
Ethyl alcohol	$CH_3.CH_2OH$
Isopropyl alcohol	$(CH_3):CHOH$
Propyl alcohol	$CH_3.CH_2.CH_2OH$
Tertiary butyl alcohol	$(CH_3)_3:COH$
Secondary butyl alcohol	$CH_3.CH_2.CH(OH).CH_3$
Primary isobutyl alcohol	$(CH_3)_2:CH.CH_2OH$
Normal butyl alcohol	$CH_3CH_2.CH_2.CH_2OH$

They found that the depressant power of these alcohols on the heart of the tortoise corresponds closely with their narcotic action on the heart of the tadpole. The order of the depressant and narcotic action increases with the increase in molecular weight in the order given above. In some cases the molecular weights are the same as is seen in the isomeric butyl alcohols. In studying these and other compounds we find that the toxicity in a homologous series increases with the length of the chain. Normal butyl alcohol is more toxic than isobutyl alcohol, isobutyl alcohol greater than secondary butyl alcohol, secondary butyl alcohol more toxic than tertiary butyl alcohol. The weakest of the butyl alcohols, however, has greater toxicity than normal propyl alcohol proving that in a homologous series molecular weight must be considered as well as the weight of the chain.

This shows a relative degree of toxicity in a homologous series whether we are studying alcohols—ethers—aldehydes, or any other class of compounds. These are the properties which are known about the alkyl radicles whether they are in combination with open-chain or closed-chain compounds. The monohydroxy alcohols were chosen in every case to show the relationship of the molecular weight and the length of the chain of the alkyl radicles to their degree of activity. Let us consider the hydrocarbon hexane which has enough carbon atoms to show the influence of the OH group upon this class of compounds. Hexane has strong anæsthetic action. Upon introducing an OH group we lessen that degree of activity though hexyl alcohol still has strong narcotic activity. Every additional OH group lessens its degree of activity and by the time we have introduced six OH groups we have Mannit $C_6H_8(OH)_6$ which has very little activity as a drug.

This is also true of the aldehydes, for example acetaldehyde CH_3CHO a hypnotic which yields aldol, $CH_3CH\begin{cases}OH\\CH_2.CHO\end{cases}$, upon condensation that has one OH group and therapeutically merely a weak hypnotic action while the aldoses like grape sugar $C_6H_{12}O_6$ which may have five OH groups have no hypnotic properties at all. These examples show in a small way the relationship of chemical structure to pharmacological action.

Summarizing briefly the most important lessons that should be taught in giving the structural formulas of drugs are to have the students read in these formulas something about their chemical properties, their physical properties and their relationship to pharmacological action.

SOURCES OF GENERAL INFORMATION.

S. Fraenkel, "Die Arzneimittel Synthese" 5th ed; Berlin 1921.
Reid, "Introduction to Organic Research."
Perkin and Kipping, "Organic Chemistry."

GREEK PHARMACEUTICAL REGULATIONS.

The problem confronting American pharmaceutical manufacturers in marketing their products in Greece is summarized herewith. There have been enacted in Greece since 1914 several decrees regulating the importation of pharmaceutical products, each differing from the other; as administered, however, the actual requirements are either: (1) Inspection and analysis by the Greek authorities, subject to fees amounting to a total of about $27 on each product; (2) the granting of a license without fee, if the importer presents a document evidencing that the product is approved by the Federal authorities of the country of origin, which document must be certified by Consular authorities (the regulations do not specify whether certificates by the U. S. Consul General in Greece or by the Greek Consul General in the U. S. are required; presumably the latter).

It has become clear through the efforts of the commercial attaché in Athens toward solving this problem that the Greek authorities require under Item 2 for products of the United States a certificate from our Bureau of Chemistry and Soils, but this Bureau has no authority under the law to issue any statements regarding the acceptability of pharmaceutical products under the Federal regulations, or regarding their free sale in this country.