of any anæsthetic effect of either ascending or decending sensory or motor fibers were noted even after prolonged application of Baptisia.

Only small percentages of Baptisia are generally incorporated into mouth washes or dentifrices. The antiseptic properties of Baptisia in such low dilutions (1%) could be *a priori* discounted. Nevertheless, definite proof of the non-antiseptic and non-germicidal properties of Baptisia infusion and Baptisia decoction were not lacking. It was noted in a few days that the infusion and decoction of Baptisia standing at room temperature became cloudy, due to the presence of micro-organisms. This indicated that even a pure or strong infusion and decoction were not antiseptic. An examination of these solutions kindly made by Dr. G. F. Reddish, Bacteriologist to this Institution, proved that the solutions were full of various bacteria.

SUMMARY.

It is thus evident that while Baptisia solutions are quite poisonous for various animals they do not exhibit any important pharmacological or therapeutic properties as far as the authors could ascertain. Such solutions were neither antiseptic nor locally anæsthetic. The rational use of such solutions is, therefore, very questionable.

REFERENCES.

(1) "Kraemer's Pharmacognosy," Philadelphia, p. 412 (1915).
(2) Husemann and Marmé, *Zft. f. Chemie.*, Vol. 1, p. 161 (1865).
(3) Partheil, *Berichte*, Vol. 33, p. 3021 (1890).
(4) Kobert, "Intoxikationen," Vol. II, p. 1175.
(5) Gray, *Edinburgh Med. J.*, Vol., 7 p. 908 (1862).
(6) Dale and Laidlaw, *J. Pharmacol.*, Vol. 3, p. 205 (1912).
(7) Radziwillowicz, *Dorpat. Ab.*, Vol. 2, p. 56 (1888).
(8) Marmé, *Göttinger gelehrte Nachrichten*, No. 24 (1871) and No. 7 (1887).
(9) Blythe, "Poisons," London, p. 406 (1920).
(10) Vallance, *Brit. Med. J.* (1875).

PHARMACOLOGICAL AND PHARMACEUTICAL
RESEARCH LABORATORIES,
HYNSON, WESTCOTT AND DUNNING.

A PHASE OF THE RELATIONSHIP OF CHEMICAL STRUCTURE TO PHARMACOLOGICAL ACTION.*

BY CHARLES W. BAUER.[1]

A discussion of the influence of an acid radicle that renders a drug water-soluble on its degree of toxicity.

Pharmacologists have given enough experimental evidence on the actions of drugs of known chemical composition that the manufacturing organic chemists have found the story of drug action written in the structural formula.

The pharmaceutical-synthetic chemist analyzes the need of the physician, goes to the laboratory and manufactures accordingly. He is interested in manu-

* Scientific Section, A. PH. A., St. Louis meeting, 1927.

[1] Professor of Organic Chemistry, Creighton College of Pharmacy, Creighton University, Omaha, Nebraska.

facturing medicinals and is concerned with the actions of radicles, nuclei and side chains, he is especially interested in the preparations that are the easiest and cheapest to prepare—their relationship to solubility and their pharmacological action.

The relationship of chemical structure to pharmacological action to be understood is necessarily studied from many angles. To the synthetic chemist one of the most important problems is, what influence will an acid radicle that renders a drug water-soluble have on its degree of toxicity? This is the problem under discussion in this paper.

Suppose we have a drug of favorable therapeutic activity, that is insoluble in water, what influence will the common radicles that are used to make drugs water-soluble have on its degree of toxicity?

Let us consider two well-known radicles—the sulpho group, SO_3H, and the carboxyl group, COOH—and their relationship to toxicity as has been worked out by leading pharmacologists. If compounds with the SO_3H or COOH group are insoluble they are usually made water-soluble by introducing an alkali metal.

Experiments by Frankel show that the degree of dissociation that an acid undergoes has no relationship to the degree of toxicity. Nitric, sulphuric and hydrochloric acids are examples of this, nitric and sulphuric acids being more toxic than hydrochloric. This holds true with organic as well as inorganic acids.

If we take phenol, C_6H_5OH, and replace the H of the OH group with an SO_3H group, a poisonous compound has been changed to a non-poisonous substance—phenyl-sulphonic ether. Phenyl-dimethyl-pyrazol, a poison, is changed to a non-poisonous compound with the SO_3H group—forming phenyldimethylpyrazol-sulphuric acid. Morphine, a very pronounced hypnotic in small doses, is transformed into a weak hypnotic as the sulphuric ether of morphine. Another example is the sulphuric ether of quinine, wholly inactive, while the action of quinine is known to all.

Nitro groups also have their toxicity reduced by the sulpho group, *e. g.*, Martius yellow changed to Naphtholgelb S.

The SO_3H has this influence on the toxicity of the phenols whether it replaces an H of the OH or replaces an H in the ring. In both cases the compound is rendered equally less toxic.

The introduction of a carboxy group and its relationship to activity and toxicity is equally interesting, *e. g.*, Cholin $(CH_3)_3{\equiv}N\begin{pmatrix}CH_2CH_2OH\\OH\end{pmatrix}$ an alcohol upon being changed to the acid Betain $(CH_3)_3{\equiv}N\begin{pmatrix}CH_2COOH\\OH\end{pmatrix}$ is rendered inactive.

The influence of COOH group on aromatic hydrocarbons is shown on benzene and naphthalene.

Benzene, C_6H_6, shows pronounced toxic properties in 2–8 grain doses, while benzoic acid, C_6H_5COOH, is safe in 12–16 grain doses.

Naphthalene, $C_{10}H_8$, poisonous in fairly large doses, is rendered physiologically inactive as monocarboxy naphthalene, $C_{10}H_7COOH$.

Phenol, C_6H_5OH, poisonous in 2 grains, is rendered therapeutically inactive as

meta and hydroxybenzoic acid. The ortho hydroxybenzoic acid is active, strongly antiseptic and antipyretic in a dose from 4 to 6 grains.

Of the dihydroxybenzenes, the ortho is the strongest poison of the three, while the carboxy acid of it, protocatechuic acid, $C_6H_3(OH)_2COOH$ 1.2.3., has neither therapeutic nor toxic properties in 4-grain doses.

Pyrogallol, $C_6H_2(OH)_3$ 1.2.3., is very poisonous while its carboxy acid, gallic acid, $C_6H_2(OH_3).COOH$, is non-poisonous and has neither antiseptic nor antipyretic properties.

Many other examples can be given, but in general the aromatic hydrocarbons and phenols have their toxicity reduced by the COOH groups, *e. g.*, aniline, $C_6H_5NH_2$, has its toxicity greatly reduced when changed to aminobenzoic acid, $C_6H_4NH_2.COOH$.

The OH group reduces the activity of the aromatic amines while the addition of the carboxyl group renders them non-poisonous, *e. g.*, $C_6H_5NH_2$ is a poison, $C_6H_4NH_2OH$ 1.2 is less poisonous, while $C_6H_3NH_2OH$ COOH 1.2.3. is comparatively safe.

If we introduce a COOH group into acetanilid C_6H_5NH CH_3CO, it is transformed to monocarboxyacetanilid, $C_6H_5NHCH_2CO.COOH$, changing it from an antipyretic to a non-active substance.

Phenacetin is a prompt antipyretic in 5- to 10-grain doses while phenacetin carboxy acid has no antipyretic properties.

In rendering these compounds soluble with either the SO_3H or COOH group the physiological activity of the original substance is destroyed, but in most cases the action can be brought back by esterification. Experiments made on various alkaloids show how esterification renders inactive substances active. Benzoylecgonine, an inactive substance, is changed to the active cocaine when the methyl group is introduced.

Tyrosin is non-poisonous, but by introducing the ethyl ester and HCl a strong poison is obtained. Aracaidin, upon esterification, gives us the physiologically active arecolin.

A group that can be used to make a drug water-soluble and still retain the properties of the mother substance is the hydrochloride of the amino or glycocoll group. The action of the new compound having about the same degree of activity as the parent compound, *e. g.*, benzocain, ethylamino benzoate, $C_6H_4NH_2.COOC_2H_5$ 1.4, is insoluble and has local anæsthetic properties. Novocaine or procaine hydrochloride is *p*-aminobenzoyldiethylaminoethanol, $C_6H_4.NH_2.COO.C_2H_4.N(C_2H_5)_2.HCl$ is water-soluble and is also a local anæsthetic. Stovaine and alypine are additional examples where the amino group and the HCl render the compound water-soluble—the other groups being responsible for the drug action.

Summarizing briefly, the sulpho and carboxyl groups and their alkali salts render many compounds water-soluble but destroy their degree of activity. Many times this activity can be restored by esterification. The hydrochloride of the amino or glycocoll group renders a drug water-soluble, still retaining the desired action of the drug.

REFERENCE.

"Die Arzneimittel"—Synthese 5th ed. By Dr. Sigmund Frankel, Berlin, 1921.