

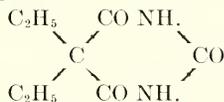
SOME THEORETICAL DISCUSSIONS OF HYPNOTICS.

THOMAS C. JALESKI, Butler University.

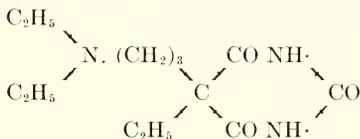
Since the pioneer work of Emil Fischer on the barbituric acids in 1904 and 1905 there has been an enormous amount of research centered about this series, due to the fact that the diethyl derivative was found to have soporific properties. The methylene hydrogen atoms of the barbituric acid ring have been replaced by a large number of alkyl and aryl groups. Substitutions have also been made in the ring, in which compounds the barbituric acids usually function in the enolic modification.

A large number of the derivatives which have been prepared have possessed remarkable hypnotic properties. Along with the soporific properties of the acids there runs another very remarkable characteristic, namely, that of possessing a very marked bitter taste. It seems very evident, however, that the bitter taste and the soporific properties do not wholly coincide.

Veronal (diethyl barbituric acid) has a faint bitter taste, and is also a very effective hypnotic.



But 5-ethyl, 5'-diethyl-amino-propyl barbituric acid has a marked bitter taste, but has no soporific properties.



The author has investigated 30 members of the series and has found that all investigated have the characteristic bitter taste.

There is, in organic compounds at the present time, apparently no constancy in the relation between chemical groups, structure, and taste. Several rules have been formulated which apply for special cases, but which are worthless when applied generally. It seemed probable that if one series was investigated thoroughly, some general conclusions could be drawn concerning the effect of different groups on taste. Taste, of course, is a complex physiological function, and the conditioning factors are so many that conclusions drawn are fraught with errors. The technique used in determining the taste must always be uniform.

It was with the idea in mind of finding out more about taste that the following diffusion experiments were conducted.

Kahlenberg¹ has recently carried on some investigations on diffusion through cholesterol membranes. He has found that the cholesterol

¹ Phil. Mag. Vol. I, 1926, p. 385.

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exhibits an ability to select materials from solution which can diffuse through the membrane. In other words, it functions as a selective membrane. He found the same true for phytosterol.

This proves to be very interesting since cholesterol is thought to be the chief constituent of the animal cell wall, and phytosterol of the plant wall. The presence of these sterols in the cell walls would account for the selective ability of the cell, according to Kahlenberg.

The work of Kahlenberg suggested the possibility of trying such membranes with hypnotics of the barbituric acid series and of thus strengthening or weakening the Meyer-Overton theory of hypnotic action. The Meyer-Overton theory states that soporific properties depend on the water lipoid solubility of the substance in question. This theory, at present the most acceptable of those current, does not seem entirely adequate.

As the source of cholesterol in the work, I used Lanolin (Merck), which is very high in cholesterol and its esters. A very fine grade of white silk was used as the membrane. This was tied over the mouth of a thistle tube and then dipped in warm Lanolin. A very uniform coating of the cholesterol may be obtained by carefully rotating the impregnated silk over a very small flame. The membrane must be tested by filling the thistle tube with nickel chloride, and placing the membrane beneath a solution of ammonium sulfide. If no nickel sulfide is formed after ten minutes the membrane can be considered tight.

Twenty cc. of a 1/10 per cent (quantitative) solution of veronal (diethyl barbituric acid) was poured into the thistle tube bearing the membrane, and the tube lowered into a beaker containing a measured amount of phosphate buffer solution having the same pH as the blood. The membrane is lowered beneath the phosphate mixture, and the diffusion is left to proceed. At intervals of two hours two cc. samples were taken from the phosphate solution, and micro Kjeldahl (Folin-Wu method) determinations were made for total nitrogen. The total nitrogen present gave directly the amount of barbituric acid which had actually diffused through the membrane.

The same was tried with the dimethyl derivative. Dimethyl barbituric acid is ineffective as a hypnotic.

Unfortunately results could not be obtained by the micro Kjeldahl method which would check from experiment to experiment. This was very likely due to impurities in the acid. They were all recrystallized several times, however. Qualitative results showed that the diethyl derivative diffused faster than the dimethyl analogue.

At present the author is working on a colorimetric determination of certain members of the barbituric acid series. If this can be worked out, the diffusion can be measured much more accurately and the diffusion of the barbituric acids into animal cells such as blood cells can be attempted. The complications which arise in using the Kjeldahl method on living cells offer too many difficulties to make the work worth trying.

It is hoped that further work on diffusion will cast some light on the theory of hypnotic action, and, indirectly, offer some explanation of the taste phenomena in the series.