those conditions in the ovaries may be much greater than in normal ovaries of guinea pigs at the time of ovulation. One single mature follicle present at the time of oestrous in the guinea pig ovary rapidly causes marked proliferation and keratinization of the epithelium of the vagina.

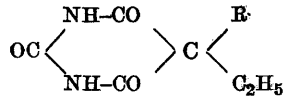
7392 C

Relationship Between Pharmacological Action and Chemical Structure of Barbituric Acid Derivatives.

EDWARD E. SWANSON. (Introduced by K. K. Chen.)

From the Lilly Research Laboratories, Indianapolis, Indiana.

To elucidate the relationship between the chemical structure and the pharmacological action in the barbital series, over 50 derivatives were investigated. These compounds were all 5,5-substituted barbituric acids, having the general formula:



wherein R-alkyl radical (normal or secondary with 2 to 9 C-atoms). Several of them were new compounds synthesized for the first time.[1]

Albino rats weighing from 71 to 126 gm. (average 96 gm.) were employed in this study. Solutions of the sodium salts of the compounds were injected intraperitoneally. The minimal anesthetic dose (M.A.D.), the duration of action, and the minimal lethal dose (M.L.D) were determined by using 5 animals for each dose level.

Since space does not permit a presentation of detailed results, only a few salient points will be discussed here. In Figs. 1 and 2, the "primary alkyls" refer to those compounds having a normal alkyl group. It should be noticed from Fig. 1 that with the increase in number of C-atoms in the alkyl group, either normal or secondary, both the M.A.D. and M.L.D. grow relatively smaller, but when the alkyl radical is longer than 5 C-atoms, the amount required to anesthetize or kill rats again increases. The therapeutic index, or the ratio between the M.L.D. and M.A.D., appears to be gradually greater as the alkyl chain lengthens.

[1] Shonle, H. A., Waldo, J. H., Keltch, A. K., and Coles, H. W., Read at the Am. Chem. Soc. Meeting, St. Petersburg, Florida, Mar. 25-30, 1934.

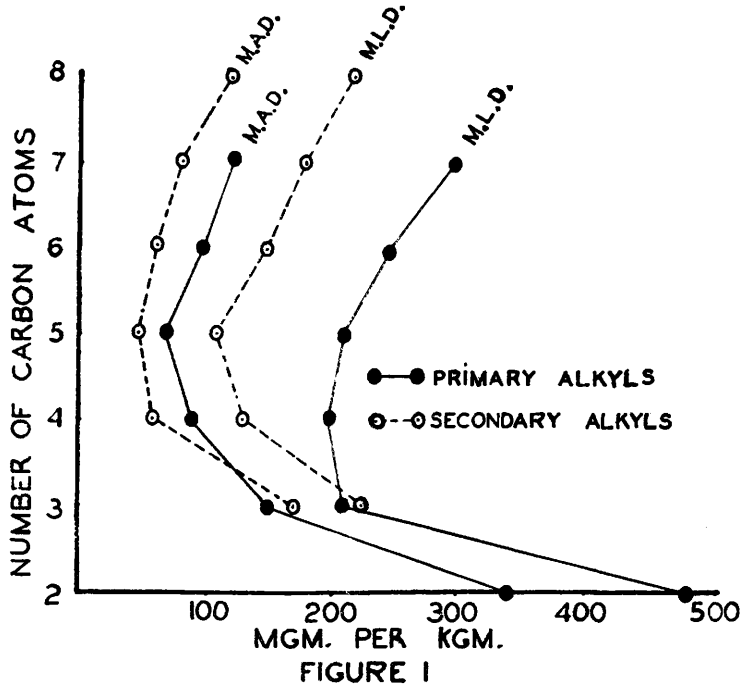


FIGURE I

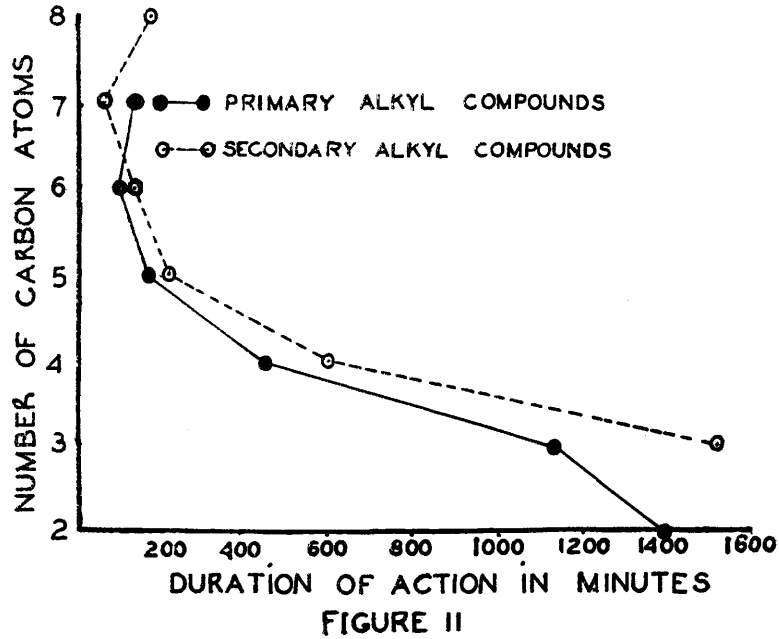


FIGURE II

In general, the duration of action shows similar features; that is, it is shorter when the alkyl group becomes lengthened (Fig. 2). In the series of normal alkyl derivatives, the critical compound is the one that possesses 6 C-atoms at R; and in the series of secondary alkyl derivatives, the critical compound is the one having 7 C-atoms at R, beyond which the duration of action begins to increase.

If R is phenyl, the compound, phenobarbital, has the well-known prolonged action; but if the ethyl group is replaced by a methyl, the resulting substance has a larger M.A.D. and M.L.D., and a shorter duration of action, as compared with phenobarbital.

The author is indebted to Dr. K. K. Chen for criticisms and assistance in the preparation of this manuscript.

7393 C

Short Acting Barbituric Acid Derivatives.

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In a previous communication,[1] it was pointed out that there is obvious relationship between the pharmacological action and the chemical structure of certain barbituric acid derivatives, and that compounds with long alkyl groups have a shorter duration of action. The present report deals with the evaluation of 12 such compounds, all of which were prepared by Shonle, Waldo, Keltch, and Coles.[2]

Typical hypnotic and anesthetic properties were observed with all the substances except one, injected intraperitoneally, in albino rats. Their minimal hypnotic doses (M.H.D.), minimal anesthetic doses (M.A.D.), and minimal lethal doses (M.L.D.) were determined, and their therapeutic indices calculated as shown in Table I. Compounds numbered 1, 2, 3, and 7 were also tested in dogs, being effective either by vein or by mouth. It is curious that compound numbered 12, 1,3-dimethyl-butyl-ethyl barbituric acid, is devoid of any hypnotic or anesthetic action, but on the contrary, produces convulsions. The substance is also highly toxic.

[1] Swanson, E. E., PROC. SOC. EXP. BIOL. AND MED. (in press).

[2] Shonle, H. A., Waldo, J. H., Keltch, A. K., and Coles, H. W., Read at the Am. Chem. Soc. Meeting, St. Petersburg, Florida, Mar. 25-30, 1934