CONCLUSIONS.

1. Digitalis in the form of properly dried crude drug has been shown to be very stable in activity over a period of six years. Air-tight and light-tight storage appears to be entirely unnecessary. There is some indication that defatting slightly improves its stability.

2. An appreciable amount of the original activity of perfectly fresh drug (about 25%) apparently may be lost during commercial drying.

REFERENCES.

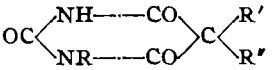
(1) Van Wijngaarden, *Arch. exptl. Path. Pharmakol.*, 113, 40 (1926).
(2) Chapman and Morrell, *Canadian Med. Assoc. J.*, 31, 400 (1934).

NITROGEN-ALKYL BARBITURIC ACID DERIVATIVES.*

BY EDWARD E. SWANSON.[1]

In a previous communication (1), it was observed that there is obvious relationship between the pharmacological action and the chemical structure of certain barbituric acid derivatives. In the primary or secondary alkyl substituted compounds, with an increase in the number of C-atoms in the alkyl group, both the minimal anesthetic dose (M. A. D.) and the minimal lethal dose (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. As the alkyl chain lengthens the therapeutic index, or the ratio between M. L. D. and M. A. D. appears to be gradually greater, the duration of action becomes shorter.

The present investigation deals with the evaluation of a number of new nitrogen alkyl substituted barbituric acid derivatives synthesized by Shonle and Doran (2) with the general formula:



wherein R-alkyl radical (methyl or ethyl), R′-alkyl (*n*-amyl, 1-methyl butyl, iso-amyl, iso-butyl, 1-methyl propyl or 1-methyl pentyl) and R″-alkyl (methyl, ethyl or allyl). Several members of these groups have been prepared by Volwiler and Tabern (3).

Albino rats weighing 75 to 125 Gm. (average 97 Gm.) were used 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.

As shown in Table I, the substitution of an ethyl or methyl radical in place of the hydrogen on the nitrogen distinctly shortens the duration of action. With an ethyl group in place of the methyl group on the nitrogen, as shown in Table I, the anesthetic dose and the lethal dose in mg. per Kg. of compounds numbered 8 and 11 are more than twice those of the methyl group on the nitrogen; however, no change in the duration of action was observed. Thus, the duration of action is not dependent on the quantity of drug administered.

---

* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] From the Lilly Research Laboratories, Indianapolis, Indiana.

TABLE I.—COMPARISON OF THE PHARMACOLOGIC ACTION OF FOURTEEN NITROGEN ALKYL BARBITURIC ACIDS.

Compound Number.	Barbituric Acids (Nitrogen Alkyl Substitution).	Number of Rats.	M. A. D. Mg. per Kg.	M. L. D. Mg. per Kg.	Duration of Action of M. A. D. (Minutes).	Therapeutic Index M. L. D. / M. A. D.
1	Nitrogen-methyl	45	140	200	600	1.42
2	" "	45	90	120	700	1.33
3[c]	" "	55	140	200	234	2.28
4	" "	13	1000	..	..	..
5[c]	" "	51	90	190	240	2.11
6	" "	13	1500	2000	280	1.50
7[a]	" "	30	60	100	60	1.66
8[a]	" ethyl	27	150	300	60	2.00
9[b]	" methyl	50	50	120	97	2.40
10	" "	55	70	140	150	2.00
11	" ethyl	36	150	340	150	2.26
12	" methyl	51	150	350	150	2.33
13	" "	46	80	170	210	2.60
14	" "	33	140	200	234	2.12

Compound Number.	Barbituric Acids (Parent Compound).	Number of Rats.	M. A. D. Mg. per Kg.	M. L. D. Mg. per Kg.	Duration of Action of M. A. D. (Minutes).	Therapeutic Index M. L. D. / M. A. D.
1	*n*-propyl-ethyl	49	150	210	1140	1.40
2	1-methyl-propyl-ethyl	35	60	130	800	2.16
3[c]	2-methyl-propyl-ethyl	35	120	220	540	1.83
4	*n*-pentyl-methyl	..	..	..	..	..
5[c]	*n*-pentyl-ethyl	50	70	210	280	3.00
6	3-methyl-butyl-methyl	21	1000	1500	580	1.50
7[a] 8[a]	3-methyl-butyl-ethyl	60	85	200	180	2.35
9[b]	1-methyl-butyl-allyl	45	40	100	186	2.50
10 11	1-methyl-butyl-ethyl	27	50	110	200	2.22
12	1-methyl-butyl-methyl	..	..	..	..	..
13	1-methyl-pentyl-allyl	35	120	220	540	1.83
14	1-methyl-pentyl-ethyl	35	60	130	600	2.16

[a] = convulsions.
[b] = tremors.
[c] = preanesthetic excitement.

CONCLUSION.

1. Fourteen alkyl nitrogen substituted barbituric acid derivatives have been studied.

2. The duration of action is distinctly reduced by the substitution of an alkyl radical on the nitrogen of barbituric acid compounds.

REFERENCES.

(1) Swanson, E. E., *Proc. Soc. Expil. Biol. Med.*, 31, 961, 964 (1934).
(2) Shonle, H. A., and Doran, W. J. (in press).
(3) Tabern, D. L., and Volwiler, E. H., *J. Am. Chem. Soc.*, April 16th Meeting, 1936.