NERVE CONDUCTIVITY.

The blood pressure and respiratory effects produced by faradization of the sciatic nerve of the dog (2 experiments) under ether anesthesia were obliterated by a sling of pinacolone. After washing with normal salt solution, nerve conductivity was restored to normal. In a rabbit's cornea (1:500) pinacolone produced hyperemia of the conjunctiva and chemosis. No perceptible local anesthetic action was observed.

DISCUSSION.

The removal of a molecule of water from tetramethylene ethylene glycol with the formation of pinacolone destroys the hypnotic properties of the former and increases its toxicity. The major pharmacologic response elicited by pinacolone is that of reducing the blood pressure, which persists after massive doses of ergotamine and decerebration. The authors attribute the depressor response to vasodilation and cardiac depression.

SUMMARY.

The pharmacology of pinacolone has been studied; as a dehydration product of pinacone it is of interest that hypnotic properties are absent.

REFERENCES.

(1) Oswald, Adolf, "Chemische Konstitution und Pharmakologische Wirkung," Berlin (1924), page 85.

(2) Marvel, C. S., Ed., "Organic Synthesis," Vol. V, John Wiley and Sons, Inc., New York City (1925) page 91.

(3) Löwen, A., *Arch. exptl. Path. Pharmakol.*, 51, 416 (1904); through Sollmann and Hanzlik.

(4) Trendelenburg, P., *Ibid.*, 63, 165 (1910); through Sollmann and Hanzlik.

THE STABILITY OF DIGITALIS POTENCY AS DRUG.*,[1]

BY L. W. ROWE AND H. W. PFEIFLE.

Many contributions can be found in the literature which deal with the stability of the active principles of liquid preparations of digitalis and the majority agree that even the highly alcoholic tincture and fluidextract at times may deteriorate rapidly. On the other hand, very little can be found about the stability of the crude drug and while some seem to take it for granted that the drug is very stable, others infer that much depends upon the conditions of storage, and that the drug can lose activity quite appreciably.

Van Wijngaarden (1) in an article on the storage of powdered digitalis leaves used the cat method exclusively for assay purposes and reported, (1) a severe loss of activity in fresh, undried digitalis leaves even in 4 or 5 days, (2) that 55° to 65° C. is the best drying temperature for the fresh leaves, (3) that the dried powder will keep at least two years without loss of activity in an ordinary stoppered flask.

Chapman and Morrell: The Potency and Standardization of Digitalis in Canada (2) make the following statement:

---

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

[1] Research Laboratories of Parke, Davis & Company, Detroit, Michigan.

"One difficulty of the manufacturer in producing and marketing tinctures of uniform strength is the fact that deterioration may occur quite rapidly. No satisfactory method of preventing this loss of strength has been proposed. *Dried leaf preparations* such as capsules are not subject to this disadvantage and from the standpoint of potency and dosage are to be recommended in preference to the tincture."

Since the cat method is not official in this country and since the opinion prevails that the dried, powdered leaves should be kept in vacuum sealed ampuls in order to insure stability of activity over long periods (this is indicated by the manner in which the International, Canadian and U. S. P. XI standard digitalis powders are put up for distribution) it was thought desirable some six years ago to begin a series of experiments with samples of leaves stored under a variety of conditions.

Accordingly a sufficient supply of the 1929 crop of Michigan grown digitalis leaves, which had been dried immediately after harvesting at a temperature of about 100° F., was set aside under several different conditions after thorough preliminary tests by the official frog method using Ouabain as the standard (U. S. P. X) had established its original activity as follows:

TABLE I.

	Product.	Date of Test.	Result as U. S. P. X Tr.
1.	Dried, chopped leaves (cutter)	1/3/30	200% of std.
2.	Dried, ground leaves	1/3/30	200% of std.
3.	Dried, defatted leaves (824,133)	1/17/30	200% of std.

Having established the relatively high potency of this lot of leaves and the fact that grinding and defatting did not alter its activity, it was then ready to be stored under the following conditions. The number of the sample as described will be used to designate it throughout the tables of data.

Sample.

1 Specially dried, finely ground and *defatted* drug which was kept at room temperature and open to the air.

2 Specially dried, finely ground and *not* defatted drug which was kept at room temperature and open to the air.

3 Ground and *defatted* drug which was kept at room temperature and open to the air. Not specially dried.

4 Ground and *not* defatted drug which was kept at room temperature and open to the air. Not specially dried.

5 Ground and *defatted* drug which was kept at room temperature in an air-tight can. Not specially dried.

6 Ground and *not* defatted drug which was kept at room temperature in an air-tight can. Not specially dried.

7 Specially dried, ground and *defatted* drug which was kept in the refrigerator and open to the air.

8 Specially dried, ground and *not* defatted drug which was kept in the refrigerator and open to the air.

9 Not specially dried. Run through cutter and not finely ground or defatted. Kept at room temperature and open to the air.

Since it may be seen from the following table that only two samples (No. 2 and No. 4) show a loss in activity at the end of six years which may be considered beyond the experimental error of the assay method, it was not thought necessary to test the samples that were held in the refrigerator during this period. It is probably signifi-

cant that the two samples which do show a 20% loss in six years of storage at room temperature were both not defatted. However, the samples kept in *air-tight* containers were no more stable in activity than those which had access to the air.

TABLE II.

Sample.	Original.	4 Mos.	8 Mos.	1 Year.	2 Years.	6 Years.
1	200%	200%	180%	200%	200%	190%
2	200%	200%	160%	180%	200%	160%
3	200%	200%	200%	200%	200%	190%
4	200%	175%	200%	165%	180%	160%
5	200%	200%	170%	180%	200%	175%
6	200%	200%	160%	200%	180%	200%
7	200%	200%	180%	200%	200%	...
8	200%	175%	180%	175%	200%	...
9	200%	...	...	...	...	190%

Since Digitalis Leaves U. S. P. XI must contain not more than 8% of moisture and Powdered Digitalis U. S. P. XI must contain not more than 5% of moisture, it was thought desirable to determine the moisture content of these eight samples at the end of six years' storage under variable conditions. Table III gives these results and shows that the powdered drug stored in air-tight cans averages about 4% of moisture which is probably about what the freshly dried and powdered drug contained originally while the average for the powdered drug which had access to the air is nearly 8% or twice as large.

TABLE III.

Sample.			Sample.		
1	7.40%	Average 7.75%	5	4.31%	Average 4.12%
2	7.29%		6	4.08%	
3	8.74%		7	3.88%	
4	7.59%		8	4.19%	

One additional example of remarkable stability of the drug when stored under adverse conditions may be cited. A display sample of unground and not defatted digitalis leaves which had been kept at room temperature in a transparent, glass-stoppered bottle for at least ten years and possibly fifteen, was extracted and its activity found to be 200% of U. S. P. X standard. Since its activity could not have been above 250% when originally placed in the bottle, it gave evidence of remarkable stability when stored under very ordinary conditions. Of course it is readily admitted that digitalis leaves should be quickly and properly dried and should be stored where they will not ferment or mold but otherwise storage in air-tight and light-tight containers appears to be entirely unnecessary.

As an example of the immediate loss of activity which occurs even when the drug is quickly and properly dried on a commercial scale the following experiment may be cited:

Perfectly fresh leaves were immediately extracted without drying and later calculation on a dry weight basis showed the activity of a regular tincture to be 400% of U. S. P. X standard. This same drug after careful and rapid commercial drying showed an activity of 300% of U. S. P. X standard so there was a loss of one-fourth of the original activity probably due to enzyme action in spite of the best precautions possible on a commercial scale.

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.

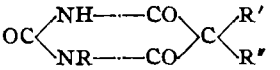
(1) Van Wijngaarden, *Arch. exptl. Path. Pharmakol.*, 113, 40 (1926).
(2) Chapman and Morrell, *Canadian Med. Assoc. J.*, 31, 400 (1934).

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.