ANESTHESIA: LII. PHARMACOLOGIC STUDY OF CERTAIN ETHINYL BARBITURATES

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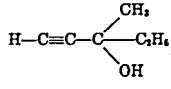
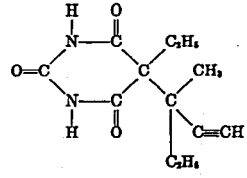
THE barbiturates occupy an enviable position among the drugs used as depressants to the central nervous system. Recently, the acetylenic derivative Dormison® (methylparafynol) (1) has been introduced as a nonbarbituric acid hypnotic. It appeared that it would be interesting to prepare for study certain barbituric acid derivatives containing the ethinyl group of Dormison in one of the positions on carbon atom "5" of the pyrimidine nucleus. The chemical relationship is shown in the following formulas:



Methylparafynol
Dormison®



5-Ethyl-5-(1,1-methylethyl-propynyl) barbituric acid
MEP

Three compounds of this type structure were synthesized for pharmacologic study.* The compounds were 5-ethyl-5-(1,1-dimethyl-propynyl barbituric acid (EPB), 5-allyl-5-(1,1-dimethylpropynyl) barbituric acid (APB), and 5-ethyl-5-(1,1-methylethylpropynyl) barbituric acid (MEP).

EXPERIMENTAL

Therapeutic Index.—The AD_{50} and the LD_{50} were determined by injecting intraperitoneally solutions of the sodium salts of the compounds into white male rats weighing between 150 and 200 Gm. MEP appeared to be the most promising of the 3 compounds. These values for MEP and pentobarbital for comparison purposes are given in

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* Prepared for us by the Ohio Chemical & Surgical Co. (a Division of Air Reduction Company, Inc.), New York, New York.

TABLE 1

ACUTE TOXICITY

Compound	LD_{50}*	AD_{50}†	T. I.‡
Pentobarbital	80 ± 8 mg./kg.	21 ± 4 mg./kg.	3.80
MEP	153 ± 31 mg./kg.	43 ± 3 mg./kg.	3.56

* LD_{50}: Median lethal dose with 95 per cent confidence limits.
† AD_{50}: Median anesthetic dose with 95 per cent confidence limits.
‡ T. I.: Therapeutic index.

table 1. EPB, like MEP, produced hypnosis in rats, but 120 mg./kg. was required. Thus, the loss of the CH_2 radical in the side chain substantially diminished the potency of the compound. Studies on APB were discontinued when preliminary observations in rats and mice showed that it elicited in the initial stages of its action a hyperreflexia with occasional clonic convulsions, though it did produce sedation.

Sleeping Time (Rats).—The induction time and the period of narcosis produced by MEP and pentobarbital were determined by intraperitoneal injections in rats. The induction time for MEP was slightly longer than that of pentobarbital (table 2); however, the duration of narcosis was considerably longer with MEP.

TABLE 2

NARCOSIS UPON INTRAPERITONEAL INJECTIONS OF MEP AND PENTOBARBITAL

Drug	Dose mg./kg.	No. of Rats	Average Induction Time, min.	Average Duration (±S.E.), min.	*P* Value
Pentobarbital	40	10	2.9	46.6 ± 3.4	
MEP	70	18	12.8	68.6 ± 4.2	<0.001

Absorption from the gastrointestinal tract was established by the oral administration of MEP sodium. In 4 animals, 180 mg./kg. produced narcosis for approximately four hours.

Effect on Blood Pressure (Dogs).—MEP and pentobarbital were compared for their effects on the blood pressure of dogs upon intravenous injections of solutions of their sodium salts. The dogs were trained to lie on their backs with minimal restraint. Blood pressure determinations were made by arterial puncture into the femoral artery and the pressures were read on a mercury manometer. The respective barbiturates were injected and continuous readings were made during the narcosis. The dosage levels were 40 mg./kg. for pentobarbital sodium and 70 mg./kg. for MEP sodium. There were 3 animals for each compound. The average blood pressure responses are shown in figure 1.

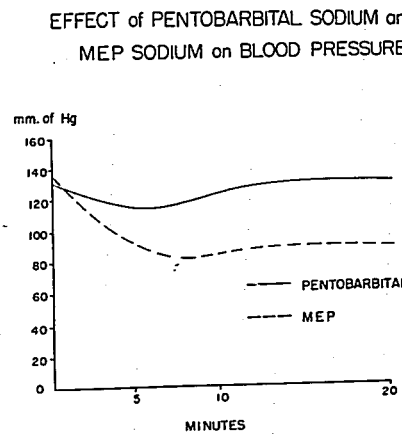

FIG. 1.

Perfused Heart (Frog).—The effect of MEP sodium was compared with that of pentobarbital sodium on the perfused frog's heart. The compounds were dissolved in Howell-Ringer's solution in concentrations of 1 to 5,000. The effects are shown in figure 2.

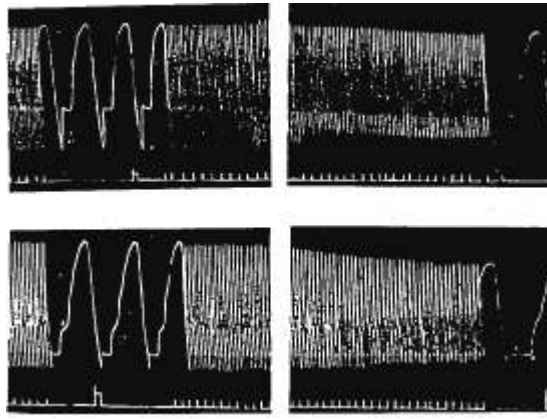

FIG. 2. Comparison of MEP sodium and pentobarbital sodium on frog heart. (*Top left*) normal; (*Top right*) 5 minutes after 20 mg. per cent (1–5,000) MEP sodium; (*Bottom left*) normal; (*Bottom right*) 5 minutes after 20 mg. per cent (1–5,000) pentobarbital sodium.

TABLE 3

PASSAGE OF CHARCOAL SUSPENSION

Drug	No. of Rats	Percentage of Intestine Through Which Charcoal Passed	P Value
Control	8	81	
Pentobarbital	8	64	0.01
MEP	9	62	0.01

Intestinal Motility.—Pentobarbital sodium and MEP sodium were compared on the intestinal motility of the rat by the method of Stickney *et al.* (2). The method depends on the relative distance traveled by a charcoal-acacia mixture from the pylorus along the intestine in a period of 40 minutes after its oral administration. The drugs were administered intraperitoneally 30 minutes prior to the charcoal suspension. The data are shown in table 3. The dosage of each drug was one-half the narcotic dosage level (20 mg./kg. pentobarbital and 30 mg./kg. MEP). Sedation was produced in the animals.

On the isolated intestinal strip of the rabbit, the relaxant action of MEP was compared with that of pentobarbital. In 3 experiments, each compound was shown to cause a reduction in tonus and a diminution of the amplitude of contractions. They appeared to be equally effective. The results in a typical experiment are shown in figure 3.

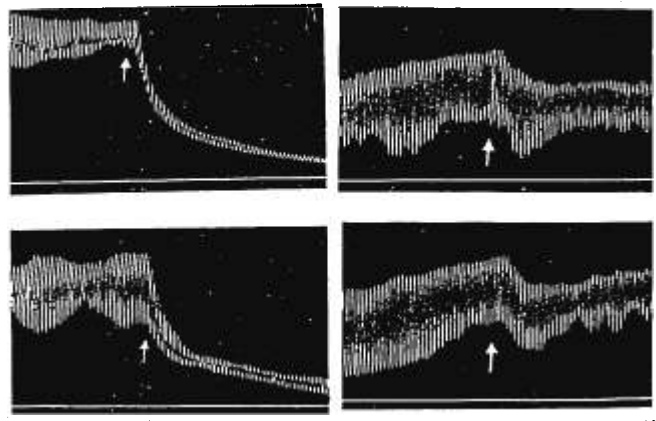

FIG. 3. Effect of pentobarbital sodium and MEP sodium on intestinal strip of rabbit. (*Top left*) Pentobarbital sodium 5×10^{-4} M; (*Top right*) pentobarbital sodium 1×10^{-4} M; (*Bottom left*) MEP sodium 5×10^{-4} M; (*Bottom right*) MEP sodium 1×10^{-4} M.

Chronic Toxicity (Rat).—Ten male white rats 150 to 170 Gm. in weight were given 40 mg./kg. of MEP orally each day for 10 days. Another group of 10 rats received 20 mg./kg. of pentobarbital sodium orally for the same time period. Their weights increased and the animals, although somewhat sedated, appeared normal. At the end of the experiment, 3 of the animals were killed and their livers, kidneys, and bone marrow subjected to histologic study. There were no abnormal findings that could be attributed to the administration of either drug. Red cell counts, white cell counts, hemoglobin percentages, urea nitrogen, and blood sugar levels were within normal limits.

Sedation in Man.—Through the kindness of Dr. David M. Kipnis, Resident in Medicine in the University Hospital, MEP was administered to a total of 19 patients. Fourteen of these individuals received the medication in doses of 50 mg. and 100 mg. as a hypnotic prior to retiring. No adverse effects such as nausea or excessive sleepiness were observed. Fifty milligrams appeared to be ineffective, whereas 100 mg. produced in these individuals approximately the same degree of sedation as did 100 mg. of pentobarbital sodium. Four patients received MEP on a dosage schedule of 50 mg. three times a day and upon retiring. There were no untoward effects nor were there any abnormal blood or urine findings. The sedative effect appears to be the equivalent of about 30 mg. of phenobarbital three times a day and at bedtime. When patients received 100 mg. upon retiring for 10 days, there were no abnormal findings in the urine or the blood, and liver function studies were within normal limits.

Discussion

These experiments with MEP indicate that this barbiturate with an ethinyl grouping in one of the "5" positions resembles the action of pentobarbital in its pharmacologic responses. Its sedative action is slower in onset and appears to be of greater duration. From animal studies and the preliminary tests in man, MEP appears to be an "intermediate acting" barbiturate similar to amobarbital sodium.

It is of interest that MEP is capable of depressing aerobic phosphorylation in rat's brain mitochondria (3).

Summary

The pharmacologic responses of a new barbiturate containing an ethinyl grouping in one of the "5" positions has been described. Preliminary trials in man indicate that the compound is useful as a hypnotic.

ADDENDUM

Since the completion of these experiments, there has appeared a paper by W. R. Gibson, E. E. Swanson, and W. J. Doran: Proc. Soc. Exper. Biol. & Med. 89: 292, 1955, on a short-acting barbiturate with an acetylenic linkage in one substituent group. Their compound is 1-methyl-5-allyl-5-(1-methylpentenyl) barbituric acid.

REFERENCES

1. Margolin, S., Perlman, P., Villari, F., and McGovack, T. H.: New Class of Hypnotics: Unsaturated Carbinols, Science 114: 384 (Oct. 12) 1951.
2. Stickney, J. C., Van Liere, E. J., and Northrup, D. W.: Correlation Between Propulsive Motility and Length of Small Intestine in Albino Rats and Dogs, Am. J. Physiol. 167: 399 (Nov.) 1951.
3. Hulme, N. A., and Krantz, J. C., Jr.: Anesthesia: Effect of Ethyl Ether on Oxidative-Phosphorylation in Brain, Anesthesiology 16: 627 (July) 1955.

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M111–M611	"Problems of Vaporization of Ether"	Lucien E. Morris, M.D.
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