# COMPARATIVE CENTRAL DEPRESSANT ACTIONS OF SOME 5-PHENYL-5-ALKYL BARBITURIC ACIDS

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## INTRODUCTION

The hypnotic actions of a considerable number of 5,5-dialkyl derivatives of barbituric acid have been studied in attempts to relate the chemical constitution of these compounds to their physiological action. Some of the earlier work with certain series of compounds led to the making of broad generalizations with regard to hypnotic effectiveness of barbituric acid derivatives. Thus, Shonle (1931) summarized previous studies of dialkyl derivatives having dissimilar alkyl groups to conclude, for example, that "in the more effective compounds, the sum of the carbon atoms on the two substituent groups was seven." Not only are exceptions to this rule now known, but Butler and Bush (1942) found none of such previously advanced rules to apply to the relative hypnotic effectiveness of the series of dialkyl derivatives that they studied. It is difficult to include the observation of Swanson (1934) that a compound like 5-(1,3-dimethyl-butyl)-5-ethyl barbituric acid in warm blooded animals is not only without effect but acts as a powerful convulsant, in any generalizations about the hypnotic effectiveness of dialkyl derivatives. Pursuing the matter of the unpredictable appearance of convulsive effects among series of these compounds, Knoefel (1945) has found examples of such convulsive effect apparently having some relation to the introduction of an unsaturated bond into the structure of the molecule and to the conversion from a barbiturate to a thiobarbiturate.

The discovery and development of the anticonvulsive effects of 5,5-diphenyl hydantoin by Merritt, Putnam and Schwab (1938) showed that hypnotic and anticonvulsant activities are not necessarily related in the actions of compounds having the hydantoin type of structure. With barbituric acid derivatives a differentiation of these two types of activities was not apparent in this work, for with pentobarbital and *iso*amyl-ethyl barbituric acid small increases in convulsive threshold were associated with dosages that produced mild hypnosis and with phenobarbital hypnotic dosages were required to cause any marked rise in the convulsive threshold. More recent studies of the anticonvulsive properties of these barbituric acids and other compounds by Tainter and coworkers (1943) led them to the conclusion that there was remarkably little difference between the dialkyl barbituric acids and phenobarbital when compared in corresponding dosages.

With regard to chemical typing of compounds used in their investigations, Merritt, Putnam and Schwab (1938) were particularly concerned with the finding

that compounds containing a phenyl group in their structure were most active as anticonvulsants. In accord with this too simple conception, Knoefel and Lehmann (1942) studied 5,5-diphenyl barbituric acid and diphenyl acetylurea as well as some other compounds containing a phenyl group, but did not find any of them to be more actively anticonvulsant than 5,5-diphenyl hydantoin. These latter workers found that large doses of diphenyl hydantoin itself are not only non-hypnotic, as had been noted by Merritt, Putnam and Schwab (1938), but actively produce convulsive phenomena as a direct response effect.

To better establish whether a notable difference in anticonvulsive activity may or may not exist between dialkyl barbitals and phenobarbital, 5-butyl-5-ethyl and 5,5-dibutyl barbituric acids were compared in the present study with 5-phenyl-5-ethyl (phenobarbital) and 5,5-diphenyl barbituric acids. Since 5,5-diphenyl hydantoin itself shows convulsant properties with considerable dosages, the convulsant 5-benzyl-5-ethyl and 5-benzyl-5-butyl barbituric acids were included for evaluation of their anticonvulsive actions. Although the studies of Merritt, Putnam and Schwab (1938) on N-phenyl and N-benzyl derivatives of barbital and our own studies (1946) on ring substituted phenobarbitals failed to demonstrate any marked anticonvulsive activity with such compounds, there were included in the present study certain 5-phenyl-5-alkyl barbituric acids.

EXPERIMENTAL. For the present investigation, commercially available 5-butyl-5-ethyl barbituric acid (neonal) and the sodium salts of 5-phenyl-5-ethyl barbituric acid (phenobarbital-sodium) and of 5,5-diphenyl hydantoin (dilantin) were used. The other required derivatives for this work were synthesized by Dr. Roland N. Icke and Dr. C. Ernst Redemann, in Pasadena. The 5,5-diphenyl barbituric acid was prepared by condensation of alloxan with benzene by following the method of Barnes and McElvain (1937). The other derivatives were prepared by developing proper methods for condensing the properly disubstituted malonic or cyanoacetic acid esters with guanidine carbonate in a sodium ethylate solution, giving the corresponding imino barbituric acids which were then acid hydrolyzed to give the desired disubstituted barbituric acids. The following compounds have not been previously described in the literature and gave the following analyses as evidence of identity and purity.

5-Phenyl-5-butyl barbituric acid
Found: C, 64.52; H, 6.57; N, 10.83 %
Calculated: C, 64.52; H, 6.25; N, 10.77 %

5-Phenyl-5-*iso*butyl barbituric acid
Found: C, 64.60; H, 6.10; N, 10.73 %
Calculated: C, 64.52; H, 6.25; N, 10.77 %

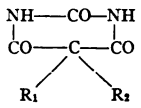
5-Phenyl-5-amyl barbituric acid
Found: C, 65.50; H, 6.58; N, 10.20 %
Calculated: C, 65.70; H, 6.62; N, 10.22 %

The other derivatives were identifiable because of their mode of synthesis and comparison of their melting points with those reported in the literature. Their melting points were often a little higher than those reported in the literature, probably because of better crystallization away from impurities.

METHODS. The methods used by the several investigators of the anticonvulsive activities of compounds in recent years have been widely divergent, and the results found have been contradictory in nature in some instances. Before 1937, and frequently since then, the experimental induction of convulsions in animals has been accomplished by injection of one of the several convulsant drugs into the animal, for example, camphor, cocaine, metrazol, picrotoxin, thujone and similar substances. The use of electrically induced convulsive responses in the study of anticonvulsant drugs, first reported by Albertoni (1882), has become common since the introduction of electroshock as a therapeutic procedure in psychiatry by Cerletti and Bini (1938). Speigel (1937) determined the convulsive reactivity of cats and rabbits by electrical stimulation through the eyeballs with an apparatus which permitted variation of both voltage and duration of an alternating current. Merritt, Putnam and Schwab (1938), Knoefel and Lehmann (1942), and Tainter and coworkers (1943) determined the convulsant threshold in terms of current strength with the

TABLE 1

*Identification of derivatives*

|  | | MELTING POINT FOUND | MELTING POINT REPORTED |
|---|---|---|---|
| | | °C. | °C. |
| Butyl | Butyl | 155–156 | 153[a] 158[b] |
| Phenyl | Propyl | 193–194 | 190[c] |
| Phenyl | Butyl | 213–214 | — |
| Phenyl | *iso*Butyl | 175–176 | — |
| Phenyl | Amyl | 171–172 | — |
| Phenyl | Hexyl | 159–160 | 152–155[d] |
| Phenyl | Phenyl | 296 | 290–292[e] |
| Benzyl | Ethyl | 211–212 | 206–207[f] |
| Benzyl | Butyl | 195 | 195[f] |

[a] Tiffeneau: Bull. soc. chim. **33**, 183, (1923).
[b] Kamm and Volwiler: U. S. #1,331,712 Feb. 24, 1920.
[c] Hoerlein: U. S. #1,025,526 May 7, 1912.
[d] Chamberlin, Doyle and Spaulding: J. Am. Chem. Soc. **57**, 352, (1935).
[e] McElvain: J. Am. Chem. Soc. **57**, 1303, (1935).
[f] Dox and Yoder: J. Am. Chem. Soc. **44**, 1141, (1922).

duration of current flow kept constant at 10 or 15 seconds. On the other hand, Kozelka, Hine and Grieber (1942) determined the convulsant threshold in terms of duration of current flow with the current kept at a constant strength, and by use of this method they were able to show threshold rises of from 2 to 10 times, while the other investigators found increases in threshold of only 1.3 to 2 times the initial level by keeping the duration constant and varying the current intensity.

In the present study the following modification of Kozelka's method has been used: The convulsive seizures were produced in rabbits by passing a 50 milliampere 60 cycle sine wave current through the head of the animal for periods of current flow ranging from a minimum of 0.05 second to as long as 30 seconds when that long a duration was found necessary. The current was applied through $\frac{3}{4}$ inch square solder covered copper electrodes held in position on the temporal region by elastic tapes. Contact was assured by using an electrode jelly. An Offner electroshock therapy apparatus was used, and because of the desirability of using shocks of durations falling between 1 and 10 seconds, as well as above 10 seconds, it was

found necessary to substitute for the resistors in the timer circuit some fixed ½ watt resistors of appropriate values to provide the desired time intervals. By this simple modification of the instrument the following shock durations were made available: 0.05, 0.1, 0.2, 0.4, 0.9, 1.8, 3.6, 7.5, 15.0 and 30.0 seconds.[1]

For routine testing the convulsant threshold was taken as the shortest duration at which a 50 milliampere current resulted in a noticeable tonic component in the convulsive response. The initial threshold for the individual rabbit was determined on the day of the test by applying a current of the fixed intensity for 0.05 second. If no tonic convulsion resulted, 15 minutes later the current was applied for 0.1 second, and so on with progressively longer durations at 15 minute intervals until the threshold was reached. The initial threshold was found to be quite constant both for the individual and between individuals. In 426 determinations made on 36 rabbits the initial threshold was found to be 0.18±0.006 seconds with a range of 0.05 to 0.9 seconds. One half hour after the threshold tonic convulsion was obtained the animal received an intraperitoneal injection of the compound to be tested and one hour after this the threshold was again determined by applying the 50 milliampere current for increasing durations from 0.05 seconds to a time value which resulted in a second tonic convulsion. A 15 minute interval between shocks was maintained throughout since investigation showed that shorter intervals were apt to be accompanied by a more or less significant depression resulting from the previous shock, whereas intervals of 15 minutes or longer were found to result in a response free from such depression. By comparing the convulsant threshold following medication with the threshold ½ hour before the injection of the test compound, the anticonvulsant activities of the several compounds were established.

In each instance the compound was injected intraperitoneally in the form of a solution of its sodium salt in water. The compound was taken into solution with a slight excess of sodium hydroxide, then the pH was adjusted to the lowest level possible (between 9.0 and 11.0) which would permit the compound to remain completely in solution, then made up to volume with distilled water. Dosage used was based on and expressed in terms of millimols per kilogram of body weight of the animal (mM/kg).

In order to establish that the depression which follows a tonic convulsion is not of sufficient magnitude to influence the results obtained by administering the drug, each animal was "standardized" by redetermining the time duration threshold without medication at 1½ hours after the initial convulsion. This value for the 33 animals so tested was found to average 0.24±0.023 seconds with a range of 0.05 to 0.4 seconds, or about 30% higher than the initial value. For evaluation of the anticonvulsant activity of the compounds a threshold time increase of 500% or 5 times the initial threshold can conservatively be insisted upon in order that the comparative evaluation of the several compounds may be unquestionable.

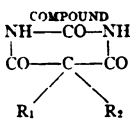
Hypnotic and lethal activities of the compounds have been determined in white mice and to some extent in rabbits. In mice, hypnosis was considered positive if righting reflexes were lacking when the animal was placed on its back, and in rabbits the end point was taken to be the inability to stand and the showing of little response when tapped briskly on the rump. In computing the hypnotic and lethal dosages the statistical method of Bliss (1938) was used throughout.

*Anticonvulsant activities.* The 12 compounds studied were found to fall into three distinct groups, as can be noted by study of table 2. Only 4 of the compounds showed marked anticonvulsant activity. These were, in order of greatest activity at a dosage of 0.2 mM/kg.: 5-phenyl-5-butyl barbituric acid (79 times the original threshold); 5-phenyl-5-propyl barbituric acid (59 times the initial

[1] We have observed that with prolonged application of current, a more or less marked depression becomes evident, and that this becomes more pronounced with the longer durations. With shocks up to 1 second the convulsant action seems to be enhanced, but with durations of 10 seconds or longer, the convulsive response is distinctly less severe.

TABLE 2

*Anticonvulsant activities of barbituric acid derivatives and dilantin on threshold for electrically induced convulsions in rabbits*

| COMPOUND  | DOSE IN mM/KG | NUMBER OF ANIMALS INJECTED | NUMBER SHOWING HYPNOSIS | NUMBER OF DEATHS | MEAN DURATION IN SECONDS OF 50 MILLIAMPERES CURRENT TO CAUSE TONIC CONVULSION | |
|---|---|---|---|---|---|---|
| | | | | | Initial | Final |
| Control | — | 33 | 0 | 0 | 0.18 | 0.24 |
| Butyl Ethyl | 0.05 | 9 | 0 | 0 | 0.13 | 0.54 |
| | 0.10 | 9 | 0 | 0 | 0.18 | 0.77 |
| | 0.20 | 16 | 11 | 0 | 0.16 | 1.25 |
| Butyl Butyl | 0.20 | 5 | 3 | 0 | 0.12 | 0.49 |
| Phenyl Ethyl | 0.05 | 23 | 0 | 0 | 0.15 | 0.63 |
| | 0.10 | 31 | 0 | 0 | 0.16 | 3.40 |
| | 0.20 | 31 | 9 | 0 | 0.18 | 11.74 |
| Phenyl Propyl | 0.05 | 13 | 0 | 0 | 0.23 | 0.66 |
| | 0.10 | 20 | 0 | 0 | 0.19 | 1.30 |
| | 0.20 | 12 | 4 | 0 | 0.21 | 11.78 |
| Phenyl *iso*Butyl | 0.05 | 11 | 0 | 0 | 0.17 | 0.56 |
| | 0.10 | 11 | 0 | 0 | 0.15 | 0.94 |
| | 0.20 | 11 | 0 | 0 | 0.15 | 11.22 |
| Phenyl Butyl | 0.025 | 12 | 0 | 0 | 0.17 | 0.58 |
| | 0.05 | 22 | 0 | 0 | 0.26 | 0.59 |
| | 0.10 | 23 | 0 | 0 | 0.22 | 4.00 |
| | 0.20 | 20 | 0 | 0 | 0.20 | 15.87 |
| | 0.40 | 4 | 1 | 0 | 0.10 | 24.38 |
| Phenyl Amyl | 0.10 | 8 | 0 | 0 | 0.25 | 0.32 |
| | 0.20 | 6 | 0 | 0 | 0.21 | 1.50 |
| Phenyl Hexyl | 0.10 | 4 | 0 | 0 | 0.20 | 0.65 |
| | 0.20 | 4 | 0 | 0 | 0.26 | 0.27 |
| Phenyl Phenyl | 0.20 | 7 | 0 | 0 | 0.13 | 0.38 |
| | 0.50 | 8 | 0 | 0 | 0.17 | 1.46 |
| Benzyl Ethyl | 0.05 | 3 | 0 | 0 | 0.16 | 0.30 |
| | 0.10 | 6 | 0 | 0 | 0.13 | 0.40 |
| | 0.20 | 9 | 4 | 0 | 0.13 | 1.43 |
| Benzyl Butyl | 0.20 | 8 | 1 | 1 | 0.12 | 0.22 |
| Dilantin | 0.05 | 11 | 0 | 0 | 0.15 | 0.55 |
| | 0.10 | 21 | 0 | 0 | 0.19 | 0.84 |
| | 0.20 | 21 | 0 | 3 | 0.17 | 1.63 |

threshold); 5-phenyl-5-ethyl barbituric acid, or phenobarbital, (58 times the initial threshold); and 5-phenyl-5-*iso*butyl barbituric acid (56 times the initial threshold). The minimal effective dose, taken as the dosage that will raise the threshold 500% or 5 times the initial threshold in 50% of the animals, has been computed for these four compounds and for 5,5-diphenyl hydantoin (dilantin) for comparison, using the statistical method of Bliss (1938) and the data is given in table 3.

A second group of compounds showed only moderate anticonvulsive activity at a dosage of 0.2 mM/kg. and included dilantin (8.2 times the initial threshold); 5-phenyl-5-amyl barbituric acid (7.5 times the initial threshold); 5-benzyl-5-ethyl barbituric acid (7.1 times the initial threshold); and 5-butyl-5-ethyl barbituric acid (6.2 times the initial threshold).

The remaining compounds were essentially inactive at a dosage of 0.2 mM/kg. These were 5-benzyl-5-butyl barbituric acid (2.4 times the initial threshold); 5,5-dibutyl barbituric acid (1.9 times the initial threshold); 5-phenyl-5-hexyl

TABLE 3

*Anticonvulsant activities of barbituric acid derivatives and dilantin*

|  | NUMBER OF RABBITS SHOWING 5 TIMES INCREASE IN DURATION THRESHOLD/NUMBER ANIMALS TESTED | | | | | ANTICONVULSANT DOSE AC-50 mM/KG |
|---|---|---|---|---|---|---|
| | Dose in mM/kg | | | | | |
| | 0.025 | 0.05 | 0.10 | 0.20 | 0.40 | |
| Phenyl Ethyl..... | — | 9/23 | 19/31 | 27/31 | — | 0.069 ±.012 |
| Phenyl Propyl..... | — | 4/13 | 11/20 | 12/12 | — | 0.083 ±.016 |
| Phenyl *iso*Butyl..... | — | 6/11 | 5/11 | 11/11 | — | 0.07 |
| Phenyl Butyl..... | 4/12 | 4/21 | 18/23 | 18/20 | 4/4 | 0.059 ±.012 |
| Dilantin..... | — | 4/11 | 5/21 | 11/21 | — | 0.279 ±.418 |

barbituric acid (1.1 times the initial threshold); and 5,5-diphenyl barbituric acid (1.3 times the initial threshold). This latter compound at a dosage of 0.5 mM/kg., exhibited a moderate anticonvulsant activity.

The marked anticonvulsant action of dilantin reported by Merritt, Putnam and Schwab (1938) and by Knoefel and Lehmann (1942) in cats has not been observed in the present investigation in rabbits. At the highest dosages used, 0.2 mM/kg. or 42.2 mg/kg., the threshold was raised by only about 8 times. Moreover, at that dosage severe symptoms of diarrhea were almost always present which lasted for about a week. In three cases death resulted within two days following dilantin intraperitoneally and in two of these the drug was certainly contributory to death, while in the other it was possible that other factors may have entered into the fatal outcome. It seems likely that rabbits are less able to tolerate the strongly basic solution than are cats. Rabbits also seem to be somewhat more resistant to showing anticonvulsant action of the drugs. It is possible that chronic dosage would have shown a greater anticonvulsant effect, but the effect of a single administration only was made the subject of the present study.

Dilantin is precipitated from a solution of its sodium salt at a pH of 9 or less, and the poor solubility of the free acid might account for the lack of response to a single intraperitoneal injection. It seems doubtful that this can entirely explain the lack of anticonvulsant activity following a single dose in view of the definite convulsant response which can be elicited with only slightly higher single doses. A similar problem is encountered with some of the less soluble barbitals used, which also are precipitated at pH 9 and so will be in the form of the free acid at the pH of the body.

*Hypnotic Activities.* The hypnotic actions of the series of compounds included in the present study are summarized for rabbits in tables 2 and 4, and are summarized for mice in table 5 after the statistical computations were made on the

TABLE 4

*Hypnotic action of barbituric acid derivatives and dilantin in rabbits following intraperitoneal injections*

|  | NUMBER OF RABBITS SHOWING HYPNOSIS/NUMBER OF RABBITS TESTED | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Dose in mM/kg | | | | | | | | |
| | 0.025 | 0.05 | 0.10 | 0.20 | 0.40 | 0.50 | 0.60 | 0.80 | 1.60 |
| Butyl Ethyl | | 0/9 | 0/9 | 11/16 | | | | | |
| Butyl Butyl | | | | 3/5 | | | | | |
| Phenyl Ethyl | | 0/23 | 0/31 | 9/31 | 2/2 | | | | |
| Phenyl Propyl | | 0/13 | 0/20 | 4/12 | | | | | |
| Phenyl *iso*Butyl | | 0/11 | 0/11 | 0/11 | | | | | |
| Phenyl Butyl | 0/12 | 0/24 | 0/25 | 0/21 | 2/10 | | 3/7 | 4/7 | 7/7(4*) |
| Phenyl Amyl | | | 0/8 | 0/6 | | | | | |
| Phenyl Hexyl | | | 0/4 | 0/4 | | | | | |
| Phenyl Phenyl | | | | 0/7 | | 0/8 | | | |
| Benzyl Ethyl | | 0/3 | 0/6 | 4/9 | | | | | |
| Benzyl Butyl | | | | 1/8(1*) | | | | | |
| Dilantin | | 0/11 | 0/21 | 0/21(3*) | | | | | |

* Number in parentheses represents the number of animals which died.

observations. With the criterion for hypnosis set at a level in rabbits at which the animal is no longer able to sit upright without vigorous prodding, it is to be observed in table 4 that at 0.2 mM/kg. the 5-butyl-5-ethyl and 5,5-dibutyl barbituric acids showed hypnosis in 69% and 60% of the animals respectively. Phenobarbital, or 5-phenyl-5-ethyl barbituric acid, showed hypnosis in 29% and 5-phenyl-5-propyl barbituric acid in 33%. In the 5-phenyl-5-alkyl series, with alkyl groups larger than propyl, the hypnotic activities at this dosage were not sufficient to meet the arbitrary criterion for hypnosis. Although none of the animals was down, a 0.2 mM/kg. dosage of 5-phenyl-5-*iso*butyl barbituric acid caused marked interference with equilibrium or obvious drowsiness in 36%, while 5-phenyl-5-butyl barbituric acid was not hypnotic at all. The 5-phenyl-5-butyl barbituric acid was hypnotic at 0.4 mM/kg. in only 20% of the animals and

at 0.8 mM/kg. in 59% as calculated from table 4. Calculation of hypnotic dose for 50% (HD-50) from these data gives about 0.7 mM/kg. for 5-phenyl-5-butyl barbituric acid, which may be compared with 0.3 mM/kg. for 5-phenyl-5-ethyl barbituric acid (phenobarbital) as reported by Shonle and Moment (1923) and confirmed by our data.

TABLE 5

*Acute toxicity and hypnotic action of barbituric acid derivatives and dilantin in Albino mice following intraperitoneal injections*

|  | NUMBER OF MICE INJECTED | HD-50 mM/KG | CD-50 mM/KG | LD-50 mM/KG |
|---|---|---|---|---|
| Butyl Ethyl | 50 | .374 ±.036 | | 1.506 ±.102 |
| Butyl Butyl | 50 | .321 ±.025 | | .967 ±.048 |
| Phenyl Ethyl | 160 | .277 ±.012 | | .954 ±.042 |
| Phenyl Propyl | 140 | .336 ±.020 | | 1.122 ±.020 |
| Phenyl *iso*Butyl | 80 | .303 ±.033 | | .978 ±.082 |
| Phenyl Butyl | 120 | .333 ±.024 | | .901 ±.010 |
| Phenyl Amyl | 140 | .459 ±.041 | | 1.301 ±.034 |
| Phenyl Hexyl | 60 | not hypnotic | | .639 ±.162 |
| Phenyl Phenyl | 140 | 1.362 ±.034 | | 2.040 ±.068 |
| Benzyl Ethyl | 60 | about .2 | about .15 | .295 ±.094 |
| Benzyl Butyl | 60 | not hypnotic | .308 ±.024 | .372 ±.023 |
| Dilantin | 30 | not hypnotic | about .40 | .985 ±.103 |

Some relation among the compounds reported in table 5 is more evident between chemical constitution and hypnotic activity in mice. The activity in the series of 5-phenyl-5-alkyl barbituric acids can be expressed as

$$\text{Ph-Et} > \text{Ph-Pr} = \text{Ph-Bu} > \text{Ph-Am} > \text{Ph-Hex}$$

and phenyl-*iso*butyl is almost as active as phenyl-ethyl. Butyl-ethyl is somewhat less active than dibutyl, and diphenyl is even less active as an hypnotic agent. The 5-benzyl-5-ethyl derivative showed a marked depressant action, but whether its action is hypnotic and similar to that of the others is not clear because of its convulsant actions.

*Convulsant activities.* Benzyl-ethyl and benzyl-butyl barbituric acids were both found to be convulsant compounds, as had been reported by Shonle and Moment (1923) for the benzyl-ethyl and benzyl-propyl compounds. However, the convulsive seizures produced by the two compounds studied are markedly different. Benzyl-ethyl barbituric acid produces a generalized clonic convulsive effect which is recurrent for hours.[2] The movements in the convulsion are very

[2] The dose-effect curve for convulsant activity following injections of 5-benzyl-5-ethyl barbituric acid is very steep. At 0.1 mM/kg. no convulsions resulted, yet at 0.2 mM/kg. all of the animals exhibited convulsive responses. This may indicate an all-or-none type of response with but little variation in threshold between individuals. With higher doses

rapid. The animal does not usually roll over on its side but drops where it is. The hind legs in particular are in an exaggerated state of extension. The respiratory muscles are not considerably involved and respiration continues quite well during the seizure. Reflex excitability is markedly exaggerated and the slightest touch is sufficient to set off a new convulsive seizure. On the other hand, depression and a kind of hypnosis are evident throughout and the animals apparently die of exhaustion.

In comparison, 5-benzyl-5-butyl barbituric acid appears to be more strychnine-like in action. The convulsive action is tonic rather than clonic and death results from the asphyxia produced by the tonic immobilization of the respiratory muscles. Autopsies performed within a short time after cessation of respiration showed the heart to beat for some time after the respiratory arrest.

Dilantin was likewise found to be convulsant at 0.4 mM/kg. in mice. The convulsions, although clonic, were neither like those from benzyl-ethyl barbituric acid nor those from benzyl-butyl barbituric acid. The animals first exhibited a period of increasing restlessness and excitement, then a spastic gait, and then showed a few clonic twitches of the neck muscles. A few minutes later these neck clonics were supplanted by a generalized tonic extensor convulsion with occasional quick clonic twitches of the legs becoming manifest. Opisthotonus was usually marked. The animal then rolled over and over. Following this a short period of depression was evident. Such convulsive response is recurrent for hours, thus after 0.5 mM/kg. of dilantin the animals were still convulsing after 3 hours, and after 1.0 mM/kg. two mice were still showing recurrent convulsions after 27 hours. In several of the rabbits following 0.2 mM/kg. of dilantin a more or less marked muscular tenseness became apparent.

*Acute toxicities.* The acute toxicities of this series of compounds have been determined on white mice kept at constant temperature of 29–30°C. during the period of observation. The statistical data are summarized with the hypnotic activities given in table 5. It will be seen that the series shows no consistent relationship between toxicity and chemical constitution unless it be that compounds having an odd number of carbon atoms in the alkyl chain are less toxic than those with an even number, but the differences are not great. It does appear that the introduction of the benzyl group makes the derivatives more toxic.

In rabbits, the LD-50 for the phenyl-butyl barbituric acid was found to be about 1.5 mM/kg. or about three times that reported by Fitch and Tatum (1932) for phenyl-ethyl barbituric acid (phenobarbital).

## DISCUSSION

The convulsions resulting from passage of a 60 cycle alternating current through the brain are typically epileptiform. Löwenbach and Lyman (1940)

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the recurrence of convulsive seizures was more prolonged, for example, 0.5 mM/kg. showed recurrences for 7 hours, while lower doses of 0.4, 0.2, and 0.15 mM/kg. showed recurrences for 4, 3 and 2 hours respectively. This may indicate an inactivation or elimination of the surplus at a fairly uniform rate to a level below the threshold required for action.

studied the influence of electroshock on the electroencephalogram in rabbits, using a 60 cycle alternating current of 25 to 35 volts with a duration of 0.1 second. As stated by Jessner and Ryan (1941), "when compared to the electroencephalograms taken during metrazol convulsions the records bore a close resemblance. The brain, once induced to discharge its energy explosively, seems to act in the same way, regardless of how the explosion is set off, and it appears that the pattern is the same for rabbit, cat and man." The anticonvulsant action of drugs must involve a mechanism which increases the resistance against irradiation of motor discharge. Just how this takes place is not clear but it apparently does not necessitate a marked depression of higher nervous centers that are productive of hypnotic action.

The demonstration by Merritt, Putnam and Schwab (1938) that 5,5-diphenyl hydantoin (dilantin) is notably anticonvulsant, yet lacks hypnotic activity, showed the necessity for formulating a new hypothesis as to the mechanism of the anticonvulsant action of hydantoin derivatives and possibly of other types of compounds. The extensive clinically successful use of dilantin for the treatment of epilepsy and related disorders in man, in doses not producing significant degrees of hypnotic action, has well substantiated the idea of differential central depressant actions for dilantin. By use of combinations of phenobarbital and amphetamine (benzedrine) in the treatment of epilepsy, Cohen and Myerson (1938) were able to demonstrate that the hypnotic action of phenobarbital could be effectively antagonized by amphetamine without apparent decrease in effectiveness for the treatment of epilepsy.

In the present investigation a number of observations support the view that two discrete mechanisms are involved in the anticonvulsant and hypnotic actions of the barbituric acid derivatives studied. Action on one of these mechanisms results in hypnosis and action on the other mechanism results in blocking the spread of nervous impulses, which if left unblocked would result in convulsive movements. That phenyl-butyl barbituric acid shows a markedly greater anticonvulsant action than phenyl-ethyl, phenyl-propyl or phenyl-*iso*butyl barbituric acids, while showing an hypnotic activity of only about $\frac{1}{3}$ that of phenyl-ethyl or $\frac{1}{2}$ that of the other two compounds, is in accord with such a concept. Butyl-ethyl barbituric acid (neonal) at 0.2 mM/kg. produced sleep in 30% of the rabbits, but only increased the threshold to electrically induced convulsions to 6 times the control level. In contrast, a dose of 0.8 mM/kg. of phenyl-butyl barbituric acid was required to produce sleep in 57% of the rabbits, yet at one-quarter that dosage, without any hypnotic effect, the convulsant threshold was increased to 79 times the control level. That the basic mechanisms for anticonvulsant and hypnotic actions are identical or interdependent is also made very improbable by the presence of both convulsions and hypnosis at the same time following administration of benzyl-ethyl barbituric acid.

The present investigation shows that the presence of a phenyl group in barbituric acid derivatives is important for the development of a considerable degree of anticonvulsant activity. The anticonvulsant activity of the butyl-alkyl derivatives studied is relatively slight. Nevertheless, the presence of a second

phenyl group decreases rather than increases this activity. With the phenyl-alkyl derivatives the anticonvulsant activity is shown only to 5 carbon atoms in the alkyl group. There is apparently a maximum of this activity in the butyl derivative and a branching of the alkyl group, as in the phenyl-*iso*butyl derivative, lessens the anticonvulsant efficiency to even somewhat less than that of the corresponding propyl compound.

It has been found by Dox and Yoder (1922), and further observed by Shonle and Moment (1923), that the presence of a benzyl group in the 5- position in certain 5-alkyl barbituric acids appears to result in marked convulsant activity. The present investigation bears this out and extends the observations to include the benzyl-butyl derivative. It is of interest to note that the hypnotic activities of the benzyl-ethyl derivative and of the isomeric phenyl-propyl derivative are almost identical. However, with regard to anticonvulsant activities, the phenyl-propyl compound is about 8 times more effective than its convulsion-producing isomer. Correspondingly, benzyl-butyl barbituric acid is about 3 times less active than the isomeric phenyl-amyl compound in anticonvulsant activity.

## SUMMARY

1. Additional evidence, from studies of the comparative central actions of dialkyl, phenyl-alkyl and diphenyl barbituric acids, is presented to show that the mechanism which raises the convulsant threshold is different from the mechanism producing hypnosis as evidenced by ataxia and drowsiness.

2. Anticonvulsant activity of barbituric acid derivatives is intensified by the presence of one 5-phenyl group, diminished by the presence of a second 5-phenyl group, and maximal with the phenyl-butyl compound in the series of phenyl-alkyl barbituric acids.

3. Among the 5-phenyl-5-alkyl barbituric acids the widest range between anticonvulsant and hypnotic activities was found to be with 5-phenyl-5-butyl barbituric acid.

4. Of the ten dialkyl and phenyl-alkyl barbituric acids studied, 5-phenyl-5-butyl barbituric acid showed the most marked anticonvulsant activity at dose levels below the hypnotic dose range.

5. The hypnotic activities of the phenyl-alkyl barbituric acids are greatest with the compounds containing the smallest alkyl groups, and this type of central depressant activity decreases with increasing size of the alkyl group.

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