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4-METHYL-4-PHENYL-5-PYRAZOLONE

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1 Claim. (Cl. 260—310)

This invention relates to 4-methyl-4-phenyl-5-pyrazolone. The novel compound possesses particular value as an anti-convulsant and is useful in the treatment of epilepsy.

Epilepsy has been defined as a cerebral dysrhythmia which may or may not be accompanied by loss of consciousness and body movements. It is now known that epileptic convulsions are related to the flow of electricity from neurons of the cerebral cortex. The type of chemical reaction which is responsible for these cerebral neuronal discharges is not known, but generally, convulsions and loss of consciousness are characterized by abnormally fast brain waves. When the patient suffers loss of consciousness and convulsions, the seizures are referred to as grand mal, a form of major epilepsy. However, convulsions do not necessarily accompany epilepsy, and in some instances consciousness is not lost. When the patient loses consciousness but convulsions are not observed, the attacks are known as petit mal. A third type of epilepsy has been clinically classified as psychomotor epilepsy.

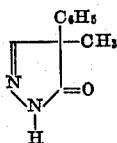
Many drugs are known which reduce or diminish epileptic seizures in man. In general, those drugs which will act as depressants of nervous transmission are effective for this purpose. The hypnotics, such as barbiturates, are effective in doses sufficient to produce anesthesia. Phenobarbital is one of the better anti-convulsants, but must be administered in hypnotic doses. The related hydantoins and oxazolidinediones have also been found to possess anti-convulsant properties. Such drugs, however, interfere to a greater or lesser extent with the normal activities of the patient.

It is most important, that any drug which is used as an anti-convulsant have very low toxicity since the nature of epilepsy requires that the patient use the drug daily and over a long period of time. The ideal anti-convulsant drug should be non-toxic, well tolerated, long acting, and devoid of sedative effects.

It is an object of this invention to provide a new compound, 4-methyl-4-phenyl-5-pyrazolone, which has a high protective index and is non-toxic in use over a long period of time.

Still another object of this invention is to provide a new compound for use in the treatment of epilepsy.

The present invention is particularly concerned with the compound 4-methyl-4-phenyl-5-pyrazolone having the structure



It has been found that the aforesaid compound has unexpected and unobvious properties of great value in combating epilepsy. This compound may take the form of tablets, powders, capsules, or other dosage forms

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which will be particularly useful for oral ingestion. The active material, namely the 4-methyl-4-phenyl-5-pyrazolone, may be admixed with solid diluents and/or tableting adjuvants such as corn starch, sucrose, lactose, magnesium stearate, talc, aluminum hydroxide, calcium carbonate; gums such as acacia, or the like. Any of the tableting materials used in pharmaceutical practice may be employed where there is no incompatibility with the 4-methyl-4-phenyl-5-pyrazolone. The material may be placed in a gelatin capsule and administered in that form. Alternatively, the compound may be emulsified in a liquid in which it is not soluble.

Anti-convulsant drugs may be assayed in the laboratory by the minimum electro-shock method. In this procedure, the drug is administered orally to the animals under test. After one hour, the animal is subjected to the direct-current stimulus that is approximately equal to three times the current necessary to produce maximum seizures. The effectiveness of various 3- and 4-substituted-5-pyrazolones as anti-convulsants is summarized in Table I. In this table, the first column gives the effective dose in milligrams per kilogram required to prevent convulsions in one-half of the animals subjected to the minimum electro-shock procedure. The second column indicates the amount of drug in milligrams per kilogram that produced neurological toxic symptoms in one-half of the experimental group. The third column of this table reports the amount of drug, again in milligrams per kilogram, that was fatal to fifty percent of the test group. Column 4 indicates the protective index (N. T. $S_{50} \div ED_{50}$).

TABLE I

	ED ₅₀	NTS ₅₀	LD ₅₀	P.I.
3-undecyl.....	800+	-----	1,000	-----
3-dodecyl.....	800+	-----	1,000	-----
4-dodecyl.....	800+	-----	1,000	-----
4,4-dimethyl.....	800+	-----	800	-----
4,4-dibutyl.....	<1,000	500	-----	-----
4-phenyl-4-methyl.....	89	187	-----	2.1

It will be noted that only a single member of the group investigated had a useful protective index.

Example I

4-METHYL-4-PHENYL-5-PYRAZOLONE

A solution of 4.3 grams (0.021 mole) of ethyl- α -formyl- α -methylphenylacetate, 8.4 milliliters of acetic acid and 3.6 grams of 85% hydrazine hydrate in 300 milliliters of absolute ethanol is refluxed for 14 hours, with condensed ethanol being percolated through a Soxhlet thimble containing 40 grams of calcium oxide before returning to the reaction flask. The alcohol solution is filtered and concentrated under vacuum to a volume of 25 milliliters and diluted with 50 milliliters of water to cause separation of an oily solid which is leached with 300 milliliters of boiling heptane and filtered. The filtrate is evaporated to 60 milliliters to cause crystallization of a pale yellow solid which subsequently is recrystallized from an acetone-heptane mixture to yield 0.8 gram (22%) of white flakes which melted at 99–101° C. Calcd. for C₁₀H₁₀N₂O: N, 16.08. Found N, 15.87.

The percentage of 4-methyl-4-phenyl-5-pyrazolone in compositions for the treatment of epilepsy may be varied. It is necessary that this compound constitute a portion such that suitable dosage will be obtained. The percentage of active agent may be conveniently 10% or 25% or even 50% since activity increases with the concentration of active material. Tablets containing from

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about 25 to about 50 mg. of 4-methyl-4-phenyl-5-pyrazolone are particularly useful. The following formations are intended to be illustrative only, and may be varied or modified to a considerable extent without departing from the spirit of the invention. We do not therefore intend to limit the invention to the specific embodiments herein set forth.

Example II

Calcium carbonate	G.
4-methyl-4-phenyl-5-pyrazolone	0.500
Calcium stearate	0.025
	0.050

The 4-methyl-4-phenyl-5-pyrazolone is adsorbed onto 10% of the calcium carbonate by mixing. The remaining calcium carbonate, previously granulated with water and dried, is added to this pyrazolone mixture. The calcium stearate is then added and after mixing until uniform, the mixture is compressed into tablets.

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Example III

Aluminum hydroxide	G.
Sucrose	0.300
Lactose	0.100
Gelatin solution	0.005
4-methyl-4-phenyl-5-pyrazolone	0.050
Magnesium stearate	0.005

The 4-methyl-4-phenyl-5-pyrazolone is adsorbed onto 10% of the aluminum hydroxide with mixing. The remainder of the aluminum hydroxide is then granulated with the sucrose, lactose, and gelatin solution and dried at 50° C. These granules are then mixed with the pyrazolone aluminum hydroxide composition and magnesium stearate until uniform and compressed into tablets.

What is claimed is:

The compound 4-methyl-4-phenyl-5-pyrazolone.

No references cited.