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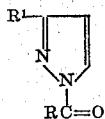
CERTAIN 1-ACYL-3-UNDECYL-PYRAZOLES

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No Drawing. Application January 13, 1958
Serial No. 708,380

4 Claims. (Cl. 260—310)

Our invention relates to 1-acyl-3-alkylpyrazoles having the structure



in which R^1 is an alkyl radical selected from the group consisting of decyl, undecyl and dodecyl radicals, and R is a member of the group consisting of acetyl and benzoyl radicals, and to a process for making these compounds. These novel compounds have anticonvulsant properties and are 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 responsive 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 the barbiturates, are effective in doses sufficient to produce anesthesia. Phenobarbital is one of the better anticonvulsants, but must be administered in hypnotic doses. The related hydantoins and oxazolidinediones have also been found to possess anticonvulsant 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 anticonvulsant 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 anticonvulsant drug should be non-toxic, well tolerated, long acting, and devoid of sedative effects.

It is a purpose of this invention to provide a method of reducing or eliminating convulsions in animals and in man by administering anticonvulsant compositions. Our new compositions are useful for veterinary purposes. Effectiveness has been found for a variety of animals, including dogs, mice, rats, and monkeys.

It is also an object of this invention to provide an efficient method for making 1-acyl derivatives of the 3-alkylpyrazoles.

It is a further object of this invention to provide an

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anticonvulsant composition in unit dosage form which has a high protective index and is non-toxic over a long period of time of use.

Still another object of this invention is to provide 1-acyl-3-alkylpyrazole compositions for use in the treatment of epilepsy.

It has been found that the aforesaid pyrazoles have unexpected and unobvious properties of great value in combatting epilepsy. These compositions may take the form of tablets, powders, capsules, or other dosage forms which will be particularly useful for oral ingestion. The compositions may take the form of active materials, namely the 1-acyl-3-alkylpyrazoles, 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 1-acyl-3-alkylpyrazoles. The material may be placed in a gelatin capsule and administered in that form. Alternatively, the 1-acyl-3-alkylpyrazole may be emulsified in a liquid in which the 1-acyl-3-alkylpyrazole is not soluble.

It has been found that only certain members of the 1-acyl-3-alkylpyrazole series have great value in combatting epilepsy. Insofar as is known, the physiological properties of the 1-acyl-3-alkylpyrazoles have not heretofore been investigated; nor have any of these compounds been applied for therapeutic purposes.

Anticonvulsant 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 a direct-current stimulus that is approximately equal to three times the current necessary to produce maximum seizures. The effectiveness of various 1-acyl-3-alkylpyrazoles as anticonvulsants 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 four indicates the protective index

$$(N.T.S._{50} \div E.D._{50})$$

and the fifth column gives the therapeutic index

$$(L.D._{50} \div E.D._{50})$$

TABLE I

	ED ₅₀	N.T.S. ₅₀	LD ₅₀	PI	TI
1-acetyl-3-undecyl-1-chloroacetyl-3-undecyl-1-benzoyl-3-decyl-1-benzoyl-3-undecyl-1-benzoyl-3-dodecyl	270 <250 75-125 130 400	ca. 1,000 >500 125-250 ca. 800 1,000	>1,200 ca. 800 500 1,000-1,250 >1,000	>3.3 >2 1-2 ca. 5.8 ca. 2.5	>4.4 >3.2 >4 7.7-9.6 2.5

The 1-acyl-3-alkylpyrazoles of this invention are prepared by treating the 3-alkylpyrazole with butyl lithium and reacting the N-lithiopyrazole so formed with an acyl halide.

EXAMPLE I

1-benzoyl-3-decylpyrazole

To a cold (0°) solution of 5.0 grams (0.024 mole) of 3-decylpyrazole in 55 milliliters of dry ether is added

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with stirring 39.5 milliliters (0.029 mole) of a 0.731 N solution of n-butyl lithium in pentane. After ten minutes, a solution of 4.2 grams (0.029 mole) of benzoyl chloride in 25 milliliters of ether is added, dropwise with stirring, over a period of ten minutes. This reaction mixture is kept at 25° for one hour and then 75 milliliters of 6% aqueous sodium bicarbonate is added and the mixture is stirred vigorously until the odor of benzoyl chloride can no longer be detected. The layers are separated and after the ether layer has been dried with magnesium sulfate, the ether solution is evaporated and the residue is distilled to give 6.2 grams (83%) of 1-benzoyl-3-decylpyrazole (boiling point 135–137° at 0.001 mm.) as a colorless viscous oil.

EXAMPLE II

1-benzoyl-3-dodecylpyrazole

To a cold (0°) solution of 5.0 grams (0.0212 mole) of 3-dodecylpyrazole in 55 milliliters of dry ether is added with stirring 37.7 milliliters (0.0254 mole) of a 0.731 N solution of n-butyl lithium in pentane. After ten minutes, a solution of 3.6 grams (0.0254 mole) of benzoyl chloride in 25 milliliters of ether is added, dropwise with stirring, over a period of ten minutes. This reaction mixture is kept at 25° C. for one hour and then 75 milliliters of 6% aqueous sodium bicarbonate is added and the mixture is stirred vigorously until the odor of benzoyl chloride can no longer be detected. The layers are separated and after the ether layer has been dried with magnesium sulfate, the ether solution is evaporated and the residue is distilled to give 5.6 grams of 1-benzoyl-3-dodecylpyrazole (boiling point 144–146° at 0.001 mm.) as a colorless liquid.

EXAMPLE III

1-acetyl-3-undecylpyrazole

To a cold (0°) solution of 10.7 grams (0.048 mole) of 3-undecylpyrazole in 110 milliliters of dry ether is added with stirring 60 milliliters (0.053 mole) of a solution of n-butyl lithium in pentane. After ten minutes, a solution of 5.7 grams (0.056 mole) of acetic anhydride in 10 milliliters of ether is added, dropwise with stirring, over a period of ten minutes. This reaction mixture is kept at 25° C. for one hour and then 150 milliliters of 6% aqueous sodium bicarbonate is added and the mixture is stirred vigorously until the odor of acetic anhydride can no longer be detected. The layers are separated and after the ether layer has been dried with magnesium sulfate, the ether solution is evaporated and the residue is distilled to give 8.5 grams of 1-acetyl-3-undecylpyrazole, a low melting solid boiling at 104–106° at 0.005 mm. This solid was recrystallized from pentane to give 6.7 grams of colorless granules (melting point 32–33° C.).

EXAMPLE IV

1-chloroacetyl-3-undecylpyrazole

To a cold (0°) solution of 10.9 grams (0.045 mole) of 3-undecylpyrazole in 110 milliliters of dry ether is added with stirring 70 milliliters (0.061 mole) of a solution of n-butyl lithium in pentane. After ten minutes, a solution of 12 grams (0.098 mole) of chloroacetyl chloride in 25 milliliters of ether is added, dropwise with stirring, over a period of ten minutes. This reaction mixture is kept at 25° C. for one hour and then 150 milliliters of 6% aqueous sodium bicarbonate is added and the mixture is stirred vigorously until the odor of chloroacetyl chloride can no longer be detected. The layers are separated and after the ether layer has been dried with magnesium sulfate, the ether solution is evaporated and the residue is distilled to give 13.5 grams of a pale yellow viscous liquid which boils at 140–145° at 0.02 mm. This liquid was dissolved in 10 milliliters of pentane and chilled at 0° C. to afford 8.3 grams of white prisms which melted at 33–34° C.

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EXAMPLE V

1-benzoyl-3-undecylpyrazole

To a cold (0°) solution of 10.7 grams (0.048 mole) of 3-undecylpyrazole in 160 milliliters of dry ether is added with stirring 60 milliliters (0.053 mole) of a solution of n-butyl lithium in pentane. After ten minutes, a solution of 7.9 grams (0.056 mole) of benzoyl chloride in 10 milliliters of ether is added, dropwise with stirring, over a period of ten minutes. This reaction mixture is kept at 25° C. for one hour and then 75 milliliters of 6% aqueous sodium bicarbonate is added and the mixture is stirred vigorously until the odor of benzoyl chloride can no longer be detected. The layers are separated and after the ether layer has been dried with magnesium sulfate, the ether solution is evaporated and the residue is distilled to give 13.3 grams 1-benzoyl-3-undecylpyrazole (boiling point 140–145° at 0.002 mm.) as a colorless oil.

The percentage of 1-acyl-3-alkylpyrazole in a pharmaceutical composition for the treatment of epilepsy may be varied. It is necessary that the active ingredient constitute a portion such that suitable dosage will be obtained. Obviously, several dosage unit forms may be administered at about the same time. Although a percentage less than 0.1% of active ingredient is effective, it is preferred to use not less than 0.1% of active agent. 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 about 25 to about 50 mg. of the 1-acyl-3-alkylpyrazole are particularly useful. The following formulations 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 this invention to the specific embodiments herein set forth.

EXAMPLE VI

Calcium carbonate	G. 0.500
1-acetyl-3-undecylpyrazole	0.005
Calcium stearate	0.050

The 1-acetyl-3-undecylpyrazole is adsorbed onto 10% of the calcium carbonate by mixing. The remaining calcium carbonate, previously granulated with water and dried, is added to this pyrazole mixture. The calcium stearate is then added and after mixing until uniform, the mixture is compressed into tablets.

EXAMPLE VII

Aluminum hydroxide	G. 0.360
Sucrose	0.100
Lactose	0.100
Gelatin solution	0.005
1-benzoyl-3-undecylpyrazole	0.050
Magnesium stearate	0.005

The 1-benzoyl-3-undecylpyrazole 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 pyrazole-aluminum hydroxide composition and magnesium stearate until uniform and compressed into tablets.

EXAMPLE VIII

Calcium carbonate	G. 0.250
Lactose	0.250
Acacia solution	0.005
1-benzoyl-3-decylpyrazole	0.050
Magnesium stearate	0.005

The 1-benzoyl-3-decylpyrazole is adsorbed onto 10% of the calcium carbonate with mixing. The remainder of the calcium carbonate is granulated with the lactose and

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acacia solution and dried at 50° C. These granules are then added with the calcium carbonate-pyrazole mixture and mixed until uniform with the magnesium stearate. The resulting product is compressed into tablets.

EXAMPLE IX

	G.
Magnesium trisilicate	0.300
Lactose	0.200
Sodium alginate solution	0.005
1-benzoyl-3-dodecylpyrazole	0.050
Magnesium stearate	0.005

The 1-benzoyl-3-dodecylpyrazole is adsorbed onto 10% of the magnesium trisilicate by mixing. The remainder of the trisilicate is granulated with the lactose and sodium alginate solution and dried at 50° C. To these granules is added the 1-benzoyl-3-dodecylpyrazole adsorbed on magnesium trisilicate and the magnesium stearate. These ingredients are mixed until uniform and compressed into tablets.

EXAMPLE X

	G.
Aluminum hydroxide	0.300
Sucrose, powdered	0.100
Lactose, powdered	0.100
1-chloroacetyl-3-undecylpyrazole	0.050
Magnesium stearate	0.005

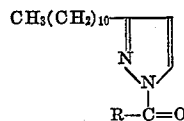
The 1-chloroacetyl-3-undecylpyrazole is adsorbed onto 10% of the aluminum hydroxide with mixing. The remainder of the aluminum hydroxide, together with the sucrose and lactose, is then added and the composition mixed until uniform. The magnesium stearate is then

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added with additional mixing and the product is filled into hard gelatin capsules.

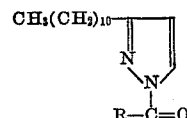
What is claimed is:

1. The compound 1-acetyl-3-undecylpyrazole.
2. The compound 1-benzoyl-3-undecylpyrazole.
3. A compound having the formula



in which R is a member of the group consisting of acetyl and benzoyl radicals.

4. A process for the preparation of a compound having the formula



in which R is a member of the group consisting of acetyl and benzoyl radicals which comprises reacting n-lithio-3-undecylpyrazole with an acyl halide selected from the group consisting of acetyl halide and benzoyl halide.

References Cited in the file of this patent

- Shirley et al.: J. Am. Chem. Soc., vol. 75, pp. 375-378 (1953).
 Kosuge et al.: Chem. Abstracts, vol. 49, col. 11628 (1955).