United States Patent Office 2,931,814 Patented Apr. 5, 1960

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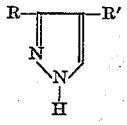
4-ALKYLPYRAZOLES

George Karmas, Somerville, N.J., assignor to Ortho Pharmaceutical Corporation, a corporation of New Jersey

No Drawing. Application April 16, 1958
Serial No. 728,769

6 Claims. (Cl. 260—310)

This invention relates to 4-alkylpyrazoles having the structure



in which R is selected from the group consisting of hydrogen and methyl radicals and R′ is an alkyl radical selected from the group consisting of heptyl, octyl, nonyl and decyl 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 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 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 4-alkylpyrazoles.

Still another object of this invention is to provide 4-alkylpyrazole compositions for use in the treatment of epilepsy.

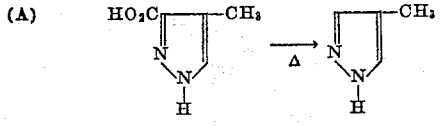
It has been found that the aforesaid pyrazoles have unexpected and unobvious properties of great value in combating epilepsy. These compositions may take the form of tablets, powders, capsules, or other dosage forms which will be particularly useful for oral ingestion. The compositions may take the form of active materials, namely the 4-alkylpyrazoles, admixed with solid diluents and/or tabletting adjuvants such as corn starch, sucrose, lactose, magnesium stearate, talc, aluminum hydroxide, calcium carbonate gums such as acacia, or the like. Any of the tabletting materials used in pharmaceutical practice may be employed where there is no incompatibility with the 4-alkylpyrazoles. The material may be placed in a gelatin capsule and administered in that form. Alternatively, the 4-alkylpyrazole may be emulsified in a liquid in which the 4-alkylpyrazole is not soluble.

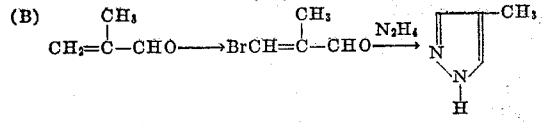
It has been found that only certain members of the 4-alkylpyrazole series have great value in combating epilepsy. Insofar as is known, the physiological properties of 4-alkylpyrazoles have not heretofore been investigated; nor have any of these compounds been applied for therapeutic purposes.

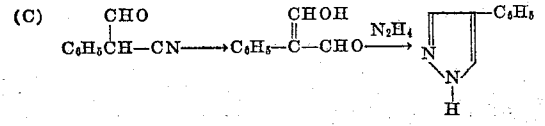
Anticonvulsant drugs may be assayed in the laboratory by the minimum electro-shock method. In this procedure, the drug is administered orally to the animals under test. After one hour, the animal is subjected to a direct-current stimulus that is approximately equal to three times the current necessary to produce maximum seizures. The effectiveness of various 4-alkylpyrazoles as anticonvulsants is summarized in the table. 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 ($N.T.D._{50} \div E.D._{50}$) and the fifth column gives the therapeutic index ($L.D._{50} \div E.D._{50}$).

Substituted Pyrazoles	ED_{50}	NTD_{50}	LD_{50}	PI	TI
4-Methyl	125	125	750–1,000	1	6+
4-Ethyl	96	110	250–500	1.1	2.6+
4-Propyl	70	125–250	250–300	1.7–3	3 5
4-Butyl	75–100	100–125	250–500	1–1.7	2.5
4-Amyl	50	125–250	250–500	2.5–5	5–10
4-Amyl-3-methyl	75–125	125–250	<500	1.3	4
4-Hexyl	~75	250–500	250–500	3.3–6.7	3.3
4-Heptyl	50	50–75	500–750	1–1.5	10–15
4-Octyl	50–75	75–125	750–1,000	1–2.5	10–15
4-Octyl-3-methyl	50–75	125–250	>500	1.7–5	ca. 10
4-Nonyl	50–75	200–250	750–1,000	3–5	10–13
4-Decyl	75	750	2,000–2,500	10	26–33
4-Decyl-3-methyl	75–125	75–125	250–500	0.5–2	2–4
4-Undecyl	∞	>1,000	>1,000	----------	--------
4-Dodecyl	∞	>1,000	>1,000	----------	--------
4-Hexadecyl	∞	>1,000	>1,000	----------	--------
4-Phenyl	~500	500–1,000	>1,000	1–2	2+
4-Phenyl-3-methyl	0 at 250	250–500	>500	----------	--------
4-Benzyl	75–100	125–250	500–750	1.2–3.3	5–7.5

The 4-alkylpyrazoles have been prepared by the following reactions:

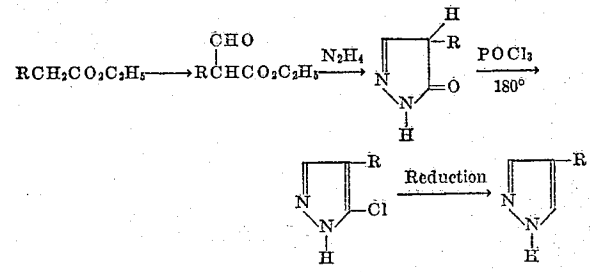






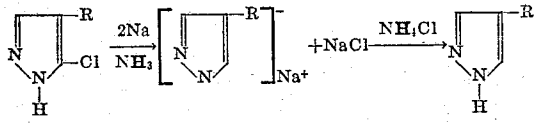
None of these syntheses is suitable for pyrazoles with the alkyl group larger than methyl because of the inaccessibility of the necessary homologous starting materials.

The 4-alkylpyrazole of the present invention may be obtained by the following sequence of reaction steps:



The reduction of the 4-alkyl-5-chloropyrazole with hydrogen and palladium to give the corresponding 4-alkylpyrazole is very troublesome requiring frequent additions of fresh catalyst and a reduction period of several days.

A superior reduction process consists of the reaction of 5-chloropyrazoles with sodium in liquid ammonia, an easily-performed procedure which always gives very high yields of the dechlorinated pyrazoles.



The synthesis involving conversion of 4-alkyl-5-pyrazolones to 4-alkyl-5-chloropyrazoles, followed by reduction to 4-alkylpyrazoles with sodium in liquid ammonia may be used for the preparation of pyrazoles in which the group at position 4 is methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, hexadecyl, phenyl and benzyl.

For a fuller understanding of the invention reference should be made to the following examples which are given as specific illustrations. It should be understood, however, that the invention is not limited to the specific details set forth in the illustrations.

EXAMPLE I.—4-HEPTYLPYRAZOLE

4-heptylpyrazolone-5

A suspension of sodium butoxide is prepared by vigorously stirring and refluxing a mixture of 25.3 grams (1.10 moles) of sodium, 145 milliliters of dry n-butanol and 1000 milliliters of toluene until evolution of hydrogen has ceased. This suspension is chilled to 5° C., 100 milliliters of dry ethyl formate is added and the mixture is stirred for ten minutes in the cold and then 200 grams (1.074 moles) of ethyl pelargonate is added. The formylation mixture is allowed to stand at 25° C., for 48 hours and then it is kept at 0° C. to 5° C., and stirred while 400 milliliters of ice water is added. The layers are separated and the toluene solution is extracted with 100 milliliters more water and then the combined aqueous solution is stirred with 300 milliliters of ether and chilled in ice while a mixture of 100 milliliters of concentrated hydrochloric acid and 100 grams of chopped ice is added rapidly to liberate the free formyl ester from its water-soluble sodium salt. After separation of layers, the aqueous phase is extracted again, with 200 milliliters of ether, and the combined ether solution is concentrated at room temperature, under waterpump vacuum, to a volume of 300 milliliters of methanol, 85 milliliters of 85% hydrazine hydrate is added, and the mixture is refluxed for two hours and then concentrated under vacuum to a solid residue of the pyrazolone. Recrystallization of the crude solid from ethanol gives 72.7 grams (37%) of 4-heptylpyrazolone-5, fine white prisms which melt at 159–160° C.

Analysis.—Calcd. for $C_{10}H_{16}N_2O$: N, 15.37. Found: N, 15.55.

4-heptyl-5-chloropyrazole

A mixture of 20 grams (0.11 mole) of 4-heptylpyrazolone-5 and 55 milliliters of phosphorus oxychloride is heated in a sealed tube at 180° C., for fifteen hours. After cooling, the tube contents are concentrated under vacuum to remove excess oxychloride and the residue is hydrolyzed on ice. The chloropyrazole is extracted with methylene dichloride after the hydrolysis mixture has been neutralized with aqueous ammonia and then the combined extracts are dried with magnesium sulfate and concentrated. Distillation of the residual oil gives 11.9 grams (54%) of 4-heptyl-5-chloropyrazole, a clear oil which boils at 115–116° C. (1.0 micron) and has n_D^{19} 1.4903.

Analysis.—Calcd. for $C_{10}H_{17}N_2Cl$: C, 59.87; H, 8.54. Found: C, 59.55; H, 8.54.

4-heptylpyrazole

A solution of 10.0 grams (0.05 mole) of 4-heptyl-5-chloropyrazole in 35 milliliters of dry ether is added with stirring to 200 milliliters of liquid ammonia. To this stirred solution is added small pieces of sodium metal until a deep blue color persists, at which point the reduction is complete. Then 6 grams of ammonium chloride is cautiously added and the excess ammonia is allowed to evaporate. Fifty milliliters of water and 100 milliliters of ether are added to the residue and, after shaking, the layers are separated and the aqueous layer is again extracted with 100 milliliters of ether. The combined ether solution is dried with magnesium sulfate and concentrated. Distillation of the residual oil gives 8.0 grams (96%) of 4-heptylpyrazole, a colorless solid which melts at 28–30° C., and boils at 95–97° C. (0.05 mm.).

Analysis.—Calcd. for $C_{10}H_{18}N_2$: C, 72.23; H, 10.92. Found: C, 72.34; H, 11.09.

EXAMPLE II.—4-OCTYLPYRAZOLE

4-octylpyrazolone-5

Crude ethyl α-formyldecanoate is prepared exactly as described in Example I, 4-heptylpyrazolone-5, using 24 grams of sodium, 140 milliliters of butanol, 1200 milliliters of toluene, 90 milliliters of ethyl formate and 200 grams (1.0 mole) of ethyl decanoate. The formyl ester is then condensed with 80 milliliters of 85% hydrazine hydrate as described in Example I, 4-heptylpyrazolone-5. The crude solid obtained on evaporation of the methanol solution is recrystallized from 400 milliliters of ethanol to give 69.7 grams (35.5%) of 4-octylpyrazolone-5, white prisms which melt at 151–153° C.

Analysis.—Calcd. for $C_{11}H_{20}N_2O$: N, 14.27. Found: N, 13.79.

4-octyl-5-chloropyrazole

Twenty grams (0.10 mole) of 4-octylpyrazolone-5 is reacted with 55 milliliters of phosphorus oxychloride exactly as described in Example I, 4-heptyl-5-chloropyrazole. After an identical working-up of the reaction mixture, distillation affords 12.6 grams (58%) of 4-octyl-5-chloropyrazole, a colorless oil which boils at 120–122° C. (1.0 micron) and has n_D^{19} 1.4881.

Analysis.—Calcd. for $C_{11}H_{19}N_2Cl$: C, 61.58; H, 8.92. Found: C, 61.76; H, 9.03.

4-octylpyrazole

The reduction of 11.9 grams (0.055 mole) of 4-octyl-5-chloropyrazole with sodium in liquid ammonia is performed and worked up exactly as described in Example I, 4-heptylpyrazole. Distillation of the product gives 9.6 grams (96%) of 4-octylpyrazole, a colorless solid which boils at 112–114° C. (0.05 mm.) and melts at 51–52° C.

Analysis.—Calcd. for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18. Found: C, 73.11; H, 11.30.

EXAMPLE III.—4-NONYLPYRAZOLE

4-nonylpyrazolone-5

Crude ethyl α-formylundecylate is prepared exactly as described in Example I, 4-heptylpyrazolone-5, using 11.3 grams of sodium, 60 milliliters of butanol, 500 milliliters of toluene, 45 milliliters of ethyl formate and 100 grams (0.467 mole) of ethyl undecylate. The formyl ester is then condensed with 35 milliliters of 85% hydrazine hydrate as described in Example I, 4-heptylpyrazolone-5. The crude solid obtained on evaporation of the methanol solution is recrystallized from 270 milliliters of ethanol to give 28.5 grams (29%) of 4-nonylpyrazolone-5, white prisms which melt at 156–157° C.

Analysis.—Calcd. for $C_{12}H_{22}N_2O$: N, 13.32. Found: N, 12.96.

4-nonyl-5-chloropyrazole

Thirteen grams (0.062 mole) of 4-nonylpyrazolone-5 is reacted with 50 milliliters of phosphorus oxychloride exactly as described in Example I, 4-heptyl-5-chloropyrazole. After an identical working-up of the reaction mixture, distillation affords 9.0 grams (64%) of 4-nonyl-5-chloropyrazole, a colorless oil which boils at 117–120° C. (1.0 micron) and has n_D^{20} 1.4879.

Analysis.—Calcd. for $C_{12}H_{21}N_2Cl$: C, 63.00; H, 9.25. Found: C, 63.07; H, 9.53.

4-nonylpyrazole

The reduction of 9.0 grams (0.039 mole) of 4-nonyl-5-chloropyrazole with sodium in liquid ammonia is performed and worked up exactly as described in Example I, 4-heptylpyrazole. Distillation of the product gives 7.5 grams (95%) of 4-nonylpyrazole, a colorless solid which boils at 105–107° C. (5 microns) and melts at 48–49° C.

Analysis.—Calcd. for $C_{12}H_{22}N_2$: C, 74.17; H, 11.42. Found: C, 74.86; H, 11.55.

EXAMPLE IV.—4-DECYLPYRAZOLE

4-decylpyrazolone-5

Crude ethyl α-formyldodecanoate is prepared exactly as described in Example I, 4-heptylpyrazolone-5, using 10.6 grams of sodium, 55 milliliters of butanol, 520 milliliters of toluene, 40 milliliters of ethyl formate, and 100 grams (0.438 mole) of ethyl dodecanoate (ethyl laurate). The formyl ester is then condensed with 30 milliliters of 85% hydrazine hydrate as described in Example I, 4-heptylpyrazolone-5. The crude solution is recrystallized from 300 milliliters of ethanol to give 28.0 grams (28%) of 4-decylpyrazolone-5, white flakes which melt at 155–156° C.

Analysis.—Calcd. for $C_{13}H_{24}N_2O$: N, 12.49. Found: N, 12.49.

4-decyl-5-chloropyrazole

Thirteen grams (0.058 mole) of 4-decylpyrazolone-5 is reacted with 50 milliliters of phosphorus oxychloride exactly as described in Example I, 4-heptyl-5-chloropyrazole. After an identical working-up of the reaction mixture, distillation affords 7.9 grams (56%) of 4-decyl-5-chloropyrazole, a colorless oil which boils at 132–135° C. (1.0 micron) and has n_D^{20} 1.4865.

Analysis.—Calcd. for $C_{13}H_{23}N_2Cl$: C, 64.27; H, 9.55. Found: C, 64.69; H, 9.54.

4-decylpyrazole

The reduction of 7.9 grams (0.0325 mole) of 4-decyl-5-chloropyrazole with sodium in liquid ammonia is performed and worked up exactly as described in Example I, 4-heptylpyrazole. Distillation of the product affords 6.7 grams (98%) of 4-decylpyrazole, a colorless solid which boils at 116–118° C. (0.05 mm.) and melts at 63–64° C.

Analysis.—Calcd. for $C_{13}H_{24}N_2$: C, 74.98; H, 11.61. Found: C, 74.93; H, 11.61.

EXAMPLE V.—3-METHYL-4-OCTYLPYRAZOLE

Seven grams (0.305 mole) of sodium is dissolved in 230 milliliters of anhydrous ethanol and the resulting solution of sodium ethoxide is stirred at 5° C., while a mixture of 61.8 milliliters (0.30 mole) of methyl nonyl ketone and 29 milliliters of ethyl formate is added within a period of thirty minutes. This formylation mixture is allowed to stand at 25° C., for sixteen hours and then it is concentrated at 30–35° C., under vacuum until most of the alcohol has been removed. The residue is shaken with 200 milliliters of pentane and 150 milliliters of ice-water to extract the sodium salt of the formylketone, and then the latter is liberated by acidification of the aqueous phase with hydrochloric acid and extraction with 300 milliliters ether. The ether extract is washed with two small portions of water, dried with magnesium sulfate and concentrated under vacuum. The crude 3-formyl-undecanone-2 thus obtained is purified by distilling it three times through a six-inch Vigreux column, collecting the desired material at 93–94° C. (1.0 mm.). This process of repeated distillation destroys by polymerization the less stable isomeric 1-formyl-undecanone-2 and affords the desired 3-formyl ketone as a white solid which is recrystallized from 30 milliliters of pentane to give 16.2 grams (27%) of fine white granules which melt at 43–44° C.

Analysis.—Calcd. for $C_{12}H_{22}O_2$: C, 72.67; H, 11.18. Found: C, 72.54; H, 11.32.

To a solution of 13.1 grams (0.066 mole) of 3-formyl-undecanone-2 in 150 milliliters of ethanol is added 4.5 milliliters of 85% hydrazine hydrate and the mixture is refluxed for two hours and then concentrated under vacuum. The residual oil is dissolved in 200 milliliters of pentane and this solution is dried with magnesium sulfate and then concentrated and the crude product is distilled to afford 3-methyl-4-octylpyrazole as a colorless oil which distills at 102–103° C. (5 microns), and has n_D^{19} 1.4812. The yield is 12.3 grams (96%).

Analysis.—Calcd. for $C_{12}H_{22}N_2$: C, 74.18; H, 11.41. Found: C, 74.64; H, 11.66.

The percentage of 4-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 4-alkylpyrazole are particularly useful. The following formulations are intended to be illus-

trative only, and may be varied or modified to a considerable extent without departing from the spirit of the invention. I do not, therefore, intend to limit this invention to the specific embodiments herein set forth.

EXAMPLE VI

	G.
Calcium carbonate	0.500
4-decylpyrazole	0.005
Calcium stearate	0.050

The 4-decylpyrazole 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

	G.
Aluminum hydroxide	0.300
Sucrose	0.100
Lactose	0.100
Gelatin solution	0.005
3-methyl-4-octylpyrazole	0.050
Magnesium stearate	0.005

The 3-methyl-4-octylpyrazole 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

	G.
Calcium carbonate	0.250
Lactose	0.250
Acacia solution	0.005
4-nonylpyrazole	0.050
Magnesium stearate	0.005

The 4-nonylpyrazole is adsorbed onto 10% of the calcium carbonate with mixing. The remainder of the calcium carbonate is granulated with the lactose and 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
4-octylpyrazole	0.050
Magnesium stearate	0.005

The 4-octylpyrazole 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 4-octylpyrazole adsorbed on magnesium trisilicate and the magnesium stearate. These ingredients are mixed until uniform and compressed into tablets.

EXAMPLE X

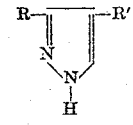
	G.
Aluminum hydroxide	0.300
Sucrose, powdered	0.100
Lactose, powdered	0.100
4-heptylpyrazole	0.050
Magnesium stearate	0.005

The 4-heptylpyrazole 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 added with additional mixing and the product is filled into hard gelatin capsules.

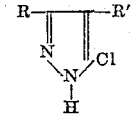
While the invention has been described with particular reference to specific embodiments, it is to be understood that it is not to be limited thereto but is to be construed broadly and restricted solely by the scope of the appended claims.

What is claimed is:

1. The compound 4-n-heptylpyrazole.
2. The compound 4-n-octylpyrazole.
3. The compound 4-n-nonylpyrazole.
4. The compound 4-n-decylpyrazole.
5. The compound 3-methyl-4-n-octylpyrazole.
6. A process for the preparation of a compound having the formula



in which R is a member of the group consisting of hydrogen and methyl radicals and R′ is a straight chain alkyl radical selected from the group consisting of heptyl, octyl, nonyl and decyl radicals which comprises reducing a compound having the formula



in which R and R′ have the meaning defined above, with metallic sodium in the presence of liquid ammonia.

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