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1-CARBAMYL AND THIOCARBAMYL-3-AMINO-4-NONSUBSTITUTED AND SUBSTITUTED PYRAZOLES

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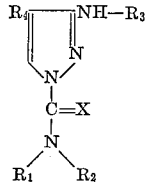
This invention relates to pyrazole derivatives and more particularly refers to 3-amino-N-carbamylpyrazoles of outstanding pharmaceutical properties.

The compounds of this invention are particularly valuable for their remarkable analgesic activity. This activity is combined with significantly high therapeutic ratios. Their outstanding and unusual combination of physiologically beneficial properties is particularly useful since the compounds so far have not shown any evidence of being addicting.

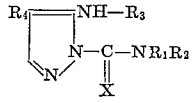
The compounds of this invention have the formula:

(1)



which can exist as the isomeric formula

(2)



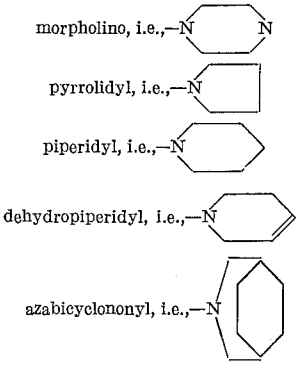
where

X is oxygen or sulfur;

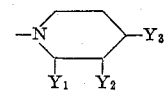
R_1 is methyl;

R_2 is alkyl of 1 through 6 carbons where the alkyl is joined to the carbamyl nitrogen by a primary or secondary carbon of the alkyl group; alken-2-yl of three through 6 carbons where the alken-2-yl group is joined to the carbamyl nitrogen by a primary or secondary carbon of the alken-2-yl group; alkoxyalkyl of 2 through 6 total carbons; hydroxyalkyl of 2 through 6 carbons; dimethyl amino; or dialkylaminoalkyl where each of the alkyl groups in the dialkyl portion has 1 or 2 carbons and the remaining alkyl group has 1 through 4 carbons with a total of from 3 through 7 in the dialkylaminoalkyl group;

and where R_1 and R_2 can be joined together and together with the carbamyl nitrogen form a heterocyclic structure from the following group:

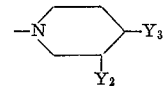


mono-substituted piperidyl of the structure



where Y_1 is H or CH_3; Y_2 is H, CH_3, C_2H_5 or $COOR_5$ where R_5 is alkyl of 1 through 4 carbons; and Y_3 is H, alkyl of 1 through 6 carbons, hydroxyalkyl of 2 through 6 carbons, trifluoromethyl, $COOR_6$ where R_6 is alkyl of 1 through 4 carbons, dialkylaminoalkyl of 3 through 7 carbons where each of the alkyl groups in the dialkyl portion has 1 or 2 carbons and the remaining alkyl group has 1 through 4 carbons, pyrrolidinoethyl or arylalkyl of 7 through 9 carbons including such groups as benzyl, phenethyl, and o-, m- and p-tolylethyl;

and disubstituted piperidyl of the structure



where Y_2 and Y_3 have the same meaning as above;

R_3 can be hydrogen but it is much more highly preferred that it is an acyl radical of 1 through 3 carbons such as formamido, acetamido and propionamido; and

R_4 is hydrogen; halogen such as fluorine, bromine and most preferably chlorine; alkyl of 1 through 3 carbons and preferably methyl; or trifluoromethyl.

Of the compounds of Formula 1 where R_2 is alkyl or alken-2-yl, it is preferred that the alkyl or alken-2-yl group is joined to the carbamyl nitrogen by a secondary carbon of the alkyl or alken-2-yl group.

The compounds of this invention are generally solids. They can can be used as inhibitors for vinyl polymerization but are particularly useful for their physiological characteristics.

Because of their excellent analgesic activity and other desirable pharmacological properties, the preferred compounds of Formula 1 are carbamyl pyrazoles where X is oxygen and where R_1 and R_2 are joined to form a piperidino ring and in particular a mono-substituted piperidyl ring where the substituent is in the para position with respect to the carbamyl nitrogen. Thus, preferred compounds of this invention include the following exemplary ones:

1-N-(4-methylpiperidino)carbonyl-3(5)-formamido-4-chloropyrazole
1-N-(4-methylpiperidino)carbonyl-3(5)-formamido-4-methylpyrazole
1-N-(4-methylpiperidino)carbonyl-3(5)-acetamido-4-chloropyrazole
1-N-(4-methylpiperidino)carbonyl-3(5)-acetamido-4-methylpyrazole
1-N-(4-methylpiperidino)carbonyl-3(5)-propionamido-4-chloropyrazole
1-N-(4-methylpiperidino)carbonyl-3(5)-propionamido-4-methylpyrazole

Also preferred are those compounds of Formula 1 where R_2 is alkyl of 1 through 4 carbons, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, etc. Illustrative of these preferred compounds are the following:

1-N,N-dimethylcarbamyl-3(5)-formamidopyrazole
3(5)-acetamido-1-N,N-dimethylcarbamylpyrazole
1-N-methyl-N-isopropylcarbamyl-3(5)-formamidopyrazole
3(5)-acetamido-1-N-methyl-N-isopropylcarbamylpyrazole
1-N-sec-butyl-N-methylcarbamyl-3(5)-formamidopyrazole

3(5) - acetamido - 1 - N - sec - butyl - N - methylcarbamylpyrazole

The substituted carbamyl pyrazoles of this invention can be prepared by reaction of the appropriate pyrazole with selected reactants as more fully described below.

When the starting material is a 3-formamidopyrazole compopnd, this latter compound can be prepared by refluxing the 3-aminopyrazole in 98–100% formic acid for at least 10 hours, removing the formic acid, and boiling the resulting product in water for 4 or more hours. The 3-acetamidopyrazoles and 3-propionamidopyrazoles are prepared by heating the 3-aminopyrazole with the appropriate anhydride for an hour, removing the excess anhydride and acid, and boiling the product for 4 or more hours.

The 4-alkyl-3-aminopyrazoles can be prepared by condensing 1 mole of the appropriate nitrile (propionitrile for methyl as the 4-alkyl) with 1 mole of ethyl formate using 1 mole of sodium ethoxide in ethanol to give the sodium salt of 2-formylpropionitrile. This latter compound is condensed with a mole of hydrazine hydrochloride by heating under reflux to obtain 3-amino-4-methylpyrazole.

3-amino-4-trifluoromethylpyrazole is prepared by treating a solution of 3-aminopyrazole-4-carboxylic acid in hydrogen fluoride with sulfur tetrafluoride at 200° C. for at least 6 hours.

One general method for the preparation of the pyrazoles of this invention can be carried out where the amine-N-carbonyl chloride e.g., N,N-dimethylcarbamoyl chloride) is available. In this process there are brought together approximately equimolar amounts of the pyrazole and the chloride in an unreactive solvent such as ether, ethyl acetate, or benzene, together with an equimolar amount of a base such as sodium hydride or triethylamine. The resulting mixture is refluxed for an extended period, say up to about 24 hours or more, and allowed to cool. The insolube chloride, e.g., sodium chloride or triethylamine hydrochloride, is filtered off and the solvent is removed from the filtrate to give the desired carbamyl or thiocarbamyl pyrazole product.

The same general procedure as just described is used when the pyrazole-1-carbonyl chloride is available (e.g., from pyrazole having hydrogen on nuclear nitrogen and either phosgene or thiophosgene) except that the secondary amine is reacted with the pyrazole carbonyl chloride. The first method is preferred if the 3-aminopyrazoles are used since the 3-amino group would react with the phosgene or thiophosgene, whereas the second method is preferred for amines such as N-methyl-N-hydroxyethylamine where the amine substituent can also react with the phosgene or thiophosgene.

The amine carbonyl chlorides such as N-piperidine carboxyl chloride are prepared by placing a flask fitted with a "Dry Ice" condenser, mechanical stirrer and dropping funnel preferably at least 1.2 moles of phosgene in an inert solvent such as ether, tetrahydrofuran, benzene, ethyl acetate or the like. A solution of 1 mole of the selected amine, e.g., piperidine, and preferably, for increased yields, with 1 mole of tertiary amine such as triethylamine, in the selected solvent is added slowly with stirring and the temperature is kept below 30° C. with occasional cooling. When all of the amine has been added, the mixture is stirred several hours. The mixture is filtered to remove the hydrochloride and the solvent is removed from the filtrate by boiling it off. The remaining amine-N-carboxyl chloride is distilled under reduced pressure to effect purification.

Alternatively, the pyrazole can be used in the above procedure in place of the amine (piperidine). By this procedure, with 3-acetamidopyrazole, one obtains 3-acetamidopyrazole-1-carbonyl chloride.

As mentioned above, the compounds of this invention have outstanding activity as analgesics, many of them exceeding codeine in potency, as shown by standard animal tests. This analgesic activity in these compounds is

particularly valuable because of significantly favorable therapeutic ratios. General painkilling benefits, as well as other physiological beneficiation associated with aspirin, are believed to be obtainable according to this invention based on tests and evaluation thus far carried out.

Furthermore, the compounds of this invention exhibit outstanding anti-inflammatory and central nervous system activity.

In pharmaceutical application a compound of this invention will be administered to the body orally, parenterally and by other methods. The dosage will vary and will depend on such factors as the condition being treated; age and weight of the recipient; the responsiveness of the recipient; prior, concurrent and intended subsequent, medication and treatment, general health of the recipient; frequency of treatment; and of course the purpose and nature of the effect desired.

Generally speaking, the active compound will be administered in a physiologically beneficial amount. Administration can be in a single dose or in a plurality of doses over an extended period of time. It will furthermore be understood that every compound within this invention does not have an identical level of dosage requirement for therapeutic or prophylactic effectiveness and therefore experts will understand that some dosage variation between compounds can be expected for maximum benefits. It will of course also be understood that an initial dose, or first group of doses, in a course of treatment can be in greater amounts, if appropriate, for a particular medical situation and a rapid response is sought by the early administration of relatively large doses and thereafter the minimally effective dosage, or maintenance dosage, is determined.

A single dose will rarely exceed about 400 or 500 milligrams of active compound within this invention, although larger amounts can be used as called for in any given situation. Extremely small doses will effect some benefit but as a practical matter a single dose of less than about 1 or 2 milligrams will seldom be used. For treating small animals with high physiological response and using highly active compounds, routine usage can be at much lower dosage levels however. Doses can be repeated in the same or greater or lesser amounts over a period of time as long as improvement in the recipient is observed or as long as needed under the circumstances.

The active compound will ordinarily be administered with a non-toxic pharmaceutical carrier in a variety of practical dosage forms. These dosage forms are novel compositions comprising the non-toxic pharmaceutical carrier and a physiologically beneficial amount of one or more active compounds of this invention. These highly useful dosage forms constitute an important aspect of the present invention.

Suitable non-toxic pharmaceutical carriers or vehicles include liquids such as water, aromatic water, alcohols, syrups, elixirs, pharmaceutical mucilages, such as acacia and tragacanth, oils such as of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil, fish oil such as cod liver oil, or the like, for oral administration; water, saline, aqueous propylene glycol, aqueous polyethylene glycol, aqueous lactose, aqueous maltose, aqueous glucose (dextrose), aqueous sucrose, or the like, for administration by injection. Suitable solid carriers include soft gelatin capsules, hard gelatin capsules, slow or delayed release pills or capsules, powders, tableting vehicles and the like. Suitable solid or liquid non-toxic pharmaceutical carriers are well known in the art and the selection of carrier can be from those appropriate and available in accordance with well known prescription techniques. The compositions of this invention therefore include such dosage forms as solution, suspensions, syrups, elixirs, tablets, capsules, powder packets, and the like.

A vast number of suitable pharmaceutical carriers are described in "Remington's Practice of Pharmacy," edited

by E. W. Martin and E. F. Cook, 12th edition, 1961, published by the Mack Publishing Company, Easton, Pennsylvania.

In these novel compositions the active ingredient of Formula 1 or 2 will be present in a physiologically beneficial amount as mentioned above. In practice this means that the active ingredient will ordinarily constitute at least about 0.01% by weight based on the total weight of the composition. For oral administration in water or other liquid medium, the concentration will ordinarily be in the range from about 0.5 to 5.0% by weight of active ingredient. For injection concentrations from 2 to 20% are satisfactory. In tablets, powders, capsules and the like the amount of active ingredient may if desired be as much as 90 to 95% or more by weight of the total composition.

The active compounds of this invention can be formulated if desired with one or more pharmaceutically active materials for combination effects, treatments and benefits. Such materials include but are by no means limited to vitamins, pain killers, tranquilizers, antibiotics, antitussive agents, etc. The compositions can of course contain suitable pharmaceutical modifiers such as coloring agents, sweetening or other flavoring agents, solubilizing agents, etc. as will readily occur to persons skilled in this art.

This invention will be better understood by reference to the following illustrative examples in which parts and percentages given are by weight unless otherwise indicated.

EXAMPLE 1

3(5)-acetamido-4-bromo-1-N,N-dimethylcarbamylpyrazole

A mixture of 10.2 grams of 4-bromo-3-acetamidopyrazole and 2.3 grams of sodium hydride in 100 milliliters of tetrahydrofuran is stirred and refluxed 15 minutes. N,N-dimethylcarbamoyl chloride (5.6 grams) is added and the mixture refluxed two hours. The mixture is filtered and the filtrate concentrated to give 13.6 grams of 3(5)-acetamido-4-bromo-1-N,N-dimethylcarbamylpyrazole. Recrystallization from benzene gives a melting point of 124–125° C.

Analysis.—Calcd. for $C_8H_{11}N_4O_2Br$: C, 34.9; H, 4.0. Found: C, 35.6; H, 4.0.

The 3-acetamido-4-bromopyrazole is obtained by the following procedure:

A solution of 16.6 grams of 3-aminopyrazole in 75 milliliters of acetic acid and 40 milliliters of acetic anhydride is heated under reflux for one hour. The solvent is removed under reduced pressure, 200 milliliters of water added, and the solution refluxed four hours and cooled. The precipitate of 3-acetamidopyrazole is collected, yield 21.3 grams, M.P. 222.5–223.5° C.

Analysis.—Calcd. for $C_5H_7N_3O$: C, 48.0; H, 5.6; N, 33.6. Found: C, 48.2; H, 5.8; N, 34.0.

To a stirred mixture of 3.0 grams of 3-acetamidopyrazole and 10 milliliters of water is added 4.0 grams of bromine. After three hours, the solution is made neutral with 10% sodium hydroxide and after some time a precipitate of 3-acetamido-4-bromopyrazole is collected (yield 3.3 grams). It is recrystallized from ethyl acetate, M.P. 144.5–145.5° C.

Analysis.—Calcd. for $C_5H_8N_3OBr$: C, 29.4; H, 3.0; Br, 39.2. Found: C, 30.7; H, 2.8; Br, 37.5.

The 3(5)-acetamido-4-bromo-1-N,N-dimethylcarbamylpyrazole of this example exhibits an outstanding combination of pharmacological properties including analgestic and anti-inflammatory activity. The compound is formulated conveniently as an injectible solution of 1%, 2%, 5% and 10% by weight concentration in a mixture of 10% ethanol and 20% propylene glycol in isotonic saline; and in 5,10, and 25 milligram amounts in standard two-piece sealed hard gelatin capsules, as well as in soft gelatin capsules, for oral administration. In pharmacological application it is administered in these dosage forms at dosage levels in the range of 5–100 milligrams.

The general procedure of the preceding example is repeated, using 4-bromo-3-acetamidopyrazole as the pyrazole reactant as in that example, and substituting on a molar basis equivalent amounts of the following indicated amine-N-carbonyl chlorides for the dimethylcarbamyl chloride of that example, to obtain the following listed exemplary compounds of this invention:

Ex. No.	Amine-N-carbonyl-chloride	Product
2	N-methyl-N-ethylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-ethylcarbamylpyrazole.
3	N-methyl-N-isopropylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-isopropylcarbamylpyrazole.
4	N-methyl-N-secbutylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-sec-butylcarbamylpyrazole.
5	N-methyl-N-n-hexylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-n-hexylcarbamylpyrazole.
6	N-methyl-N-(penten-2-yl)carbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-(penten-2-yl)carbamylpyrazole.
7	N-methyl-N-(2-hydroxyethyl)-carbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-(2-hydroxyethyl)carbamylpyrazole.
8	N-methyl-N-methyoxymethylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-methoxymethylcarbamylpyrazole.
9	N-methyl-N-methoxypropylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-methoxypropylcarbamylpyrazole.
10	N-methyl-N-dimethylaminocarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-dimethylaminocarbamylpyrazole.
11	N-methyl-N-diethylaminoethylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-diethylaminoethylcarbamylpyrazole.
12	N-methyl-N-n-propylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-n-propylcarbamylpyrazole.
13	N-methyl-N-isobutylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-isobutylcarbamylpyrazole.
14	N-methyl-N-allylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-allylcarbamylpyrazole.
15	N-methyl-N-methoxyethylcarbamoyl chloride.	3-acetamido-4-bromo-1-N-methyl-N-methoxyethylcarbamylpyrazole.

The preceding Examples 1–15 can be repeated using a similar amount of corresponding thiocarbamoyl chloride reactant in place of the indicated carbamoyl chloride reactant to obtain the corresponding thiocarbamylpyrazole products.

Similarly, the preceding procedures can be repeated using the corresponding 4-chloro, 4-fluoro, 4-alkyl and 4-trifluoromethylcarbamoyl and thiocarbamoyl chloride reactants in place of the indicated carbamoyl and thiocarbamoyl chloride reactant to obtain the corresponding carbamylpyrazole and thiocarbamylpyrazole products.

Similarly, the preceding examples can be repeated using corresponding carbamoyl and thiocarbamoyl chloride reactants having only hydrogen in the 4-position to obtain the corresponding 4-unsubstituted carbamylpyrazole and thiocarbamylpyrazole products, as illustrated by the following:

EXAMPLE 16

3-acetamido-1-N,N-dimethylcarbamylpyrazole

A mixture of 12.5 grams of 3-acetamidopyrazole and 4.7 grams of sodium hydride (53%) in 100 milliliters of the dimethyl ether of ethylene glycol are stirred and refluxed 30 minutes. N,N-Dimethylcarbamoyl chloride (10.7 grams) is added and the mixture refluxed overnight. The mixture is filtered and the filtrate evaporated to dryness. The solid remaining is recrystallized from benzene to give 12.5 grams of 1-N,N-dimethylcarbamyl-3-acetamidopyrazole, M.P. 122–124° C.

Analysis.—Calcd. for $C_8H_{12}N_4O_2$: C, 49.0; H, 6.2; N, 28.6. Found: C, 48.0; H, 6.2; N, 28.8.

The compound is formulated and used in 25, 50 and 100 milligram amounts in standard two pieced hard gelatin capsules for oral administration. The compound is formulated conveniently as injectible solutions of 5 and 10% by weight concentration in isofonic saline; and as injectible solutions in 5% and 10% by weight concentrations in an aqueous solution containing also 5% dextrose.

EXAMPLE 17

3-amino-1-N,N-dimethylcarbamylpyrazole

A mixture of 17.0 grams of 1-N,N-dimethylcarbamyl-3(5)-(p-dimethylaminobenzalamino)pyrazole, 12.5 grams of 2,4-dinitrophenylhydrazine, and 0.5 grams of p-toluenesulfonic acid in 200 milliliters of ethanol are refluxed 30 minutes, cooled in ice, and filtered. The filtrate is concentrated, dissolved in 150 milliliters of water, treated with decolorizing charcoal, and extracted overnight with chloroform in a continuous extractor. The chloroform extract is concentrated to give 6.4 grams of 3(5)-amino-1-N,N-dimethylcarbamylpyrazole, M.P. 59–62° C., which upon recrystallization from cyclohexane has a melting point of 63–64° C.

Analysis.—Calcd. for $C_6H_{10}N_4O$: C, 46.7; H, 6.5; N, 36.4. Found: C, 47.1; H, 6.4; N, 36.2.

This compound can be formulated in 10% by weight concentration in isotonic saline solution. Dosage of 50–100 milligrams as needed can be administered for analgesic and anti-inflammatory treatments.

EXAMPLE 18

1-N,N-dimethylcarbamyl-3-formamidopyrazole

A solution of 15 grams of 3-aminopyrazole in 50 milliliters of 98% formic acid is heated under reflux overnight (16 hours). The formic acid is removed under reduced pressure (7 mm.) and the residue is refluxed in 100 milliliters of water for six hours. This is cooled and the precipitate of 3-formamidopyrazole is collected to yield 10.0 grams, M.P. 160–161° C.

A mixture of 5.7 grams of 3-formamidopyrazole, 2.4 grams of sodium hydride (53% in mineral oil) and 5.3 grams of N,N-dimethylcarbamoyl chloride is stirred and heated under reflux overnight. The mixture is filtered and the filtrate is evaporated to dryness. The residue is recrystallized from benzene to give 5.25 grams of 1-N,N-dimethylcarbamyl-3-formamidopyrazole, M.P. 75–78° C.

The compound of this example has significant analgesic and anti-inflammatory activity. It is conveniently formulated in 2% by weight concentration in water together with a flavoring agent and can be taken orally in doses of from 10 to 50 milligrams each every 4 to 6 hours as needed as a codeine substitute for relief from pain.

It can also be formulated as a tablet containing from 2.5 to 50 milligram amounts, from 1–4% by weight of gelatin and from 0.5 to 1.5% by weight of a lubricant such as magnesium stearate or talc, and mannitol as a filler.

By the foregoing procedures the following examplary compounds can be obtained:

Example	Product
19	3-amino-4-chloro-1-N,N-dimethylcarbamylpyrazole.
20	3-amino-4-fluoro-1-N-methyl-N-ethylcarbamylpyrazole.
21	3-amino-4-trifluoromethyl-1-N-methyl-N-(buten-2-yl)-carbamylpyrazole.
22	3-amino-4-ethyl-1-N-methyl-N-(5-hydroxypentyl)carbamylpyrazole.
23	3-amino-4-methyl-1-N,N-dimethylthiocarbamylpyrazole.
24	3-amino-4-chloro-1-N-methyl-N-ethylthiocarbamylpyrazole.
25	3-formamido-4-chloro-1-N-methyl-N-ethylcarbamylpyrazole.
26	3-formamido-4-bromo-1-N-methyl-N-diethylaminoethylcarbamylpyrazole.
27	3-formamido-4-methyl-1-N-methyl-N-ethoxypropylthiocarbamylpyrazole.
28	3-acetamido-4-chloro-1-N,N-dimethylcarbamylpyrazole.
29	3-acetamido-4-methyl-1-N,N-dimethylcarbamylpyrazole.
30	3-acetamido-4-chloro-1-N,N-dimethylthiocarbamylpyrazole.
31	3-acetamido-4-methyl-1-N,N-dimethylthiocarbamylpyrazole.
32	3-acetamido-4-chloro-1-N-methyl-N-ethylcarbamylpyrazole.
33	3-acetamido-4-chloro-1-N-methyl-N-ethylthiocarbamylpyrazole.
34	3-acetamido-4-methyl-1-N-methyl-N-ethylcarbamylpyrazole.
35	3-acetamido-4-methyl-1-N-methyl-N-ethylthiocarbamylpyrazole.
36	3-propionamido-1-N,N-dimethylcarbamylpyrazole.
37	3-propionamide-1-N,N-dimethylthiocarbamylpyrazole.
38	3-propionamido-4-bromo-1-N,N-dimethylcarbamylpyrazole.
39	3-propionamido-4-chloro-1-N,N-dimethylcarbamylpyrazole.
40	3-propionamido-4-methyl-1-N,N-dimethylcarbamylpyrazole.
41	3-propionamido-4-trifluoromethyl-1-N-methyl-N-sec-butylcarbamylpyrazole.
42	3-formamido-4-chloro-1-N-methyl-N-n-propylcarbamylpyrazole.
43	3-formamido-4-chloro-1-N-methyl-N-n-propylthiocarbamylpyrazole.
44	3-formamido-4-methyl-1-N-methyl-N-n-propylcarbamylpyrazole.
45	3-formamido-4-bromo-1-N-methyl-N-n-propylcarbamylpyrazole.
46	3-formamido-4-bromo-1-N-methyl-N-isopropylcarbamylpyrazole.
47	3-formamido-4-chloro-1-N-methyl-N-isopropylcarbamylpyrazole.
48	3-acetamido-4-chloro-1-N-methyl-N-methoxyethylcarbamylpyrazole.
49	3-formamido-4-chloro-1-N-methyl-N-dimethylaminocarbamylpyrazole.
50	3-formamido-4-bromo-1-N-methyl-N-isobutylcarbamylpyrazole.
51	3-propionamido-4-methyl-1-N-methyl-N-allylcarbamylpyrazole.
52	3-amino-4-n-propyl-1-N-methyl-N-diethylaminoethylcarbamylpyrazole.

EXAMPLE 53

3-acetamido-1-N-piperidinocarbonylpyrazole

A mixture of 12.5 grams (0.1 mole) of 3-acetamidopyrazole and 4.7 grams of sodium hydride (53% in oil) in 200 milliliters of dimethoxy ethane is stirred and refluxed for 30 minutes. Pentamethylenecarbamoyl chloride (15.7 grams, 0.1 mole) is added in portions, and the mixture is refluxed 8 hours with stirring. The hot reaction mixture is filtered and the precipitate washed with ethyl acetate. The filtrate is cooled in ice and the precipitate is collected, yield 4.4 grams, M.P. 188–197° C. The precipitate first obtained is washed with water to remove the sodium chloride and dried, yield 14.3 grams, M.P. 202–204° C. A portion of the latter is recrystallized twice from dioxane to give pure 3-acetamido-1-N-piperidinocarbonylpyrazole, M.P. 207.5–208.5° C.

Analysis.—Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.9; H, 6.8. Found: C, 56.0; H, 7.0.

This compound can be formulated and used in 5, 10 and 50 milligram amounts in standard two piece hard gelatin capsules containing corn starch as a diluent.

The preceding example is repeated substituting other substituted pyrazoles and substituted carbamoyl and thiocarbamoyl chlorides for the reactants of that Example to obtain the following compounds:

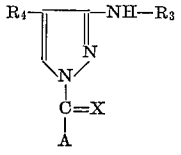
Example	Product
54	3-amino-1-N-morpholinocarbonylpyrazole.
55	3-acetamido-1-N-pyrrolidinocarbonylpyrazole.
56	3-formamido-1-N-piperidinocarbonylpyrazole.
57	3-formamido-1-N-dehydropiperidinocarbonylpyrazole.
58	3-acetamido-1-N-dehydropiperidinocarbonylpyrazole.
59	3-formamido-1-N-azabicyclononylcarbonylpyrazole.
60	3-acetamido-1-N-(3,4-dimethylpiperidino)-carbonylpyrazole.
61	3-acetamido-1-N-p-tolylethylpiperidinocarbonylpyrazole.
62	3-formamido-4-bromo-1-N-m-methylpiperidinocarbonylpyrazole.
63	3-acetamido-4-chloro-1-N-p-trifluoromethylpiperidinocarbonylpyrazole.
64	3-acetamido-4-chloro-1-N-p-ethylpiperidino(thiocarbonyl)-pyrazole.
65	3-propionamido-4-bromo-1-N-[p-(n-butyl)-piperidino]-(thiocarbonyl)pyrazole.
66	3-acetamido-4-methyl-1-N-o-methylpiperidino-(thiocarbonyl)pyrazole.
67	3-formamido-4-chloro-1-N-p-benzylpiperidinocarbonylpyrazole.
68	3-acetamido-4-chloro-1-N-(m-ethoxycarbonylpiperidino)-carbonylpyrazole.
69	3-acetamido-4-chloro-1-N-dehydropiperidinocarbonylpyrazole.
70	3-formamido-4-chloro-1-N-(3-methyl-4-ethylpiperidino)-carbonylpyrazole.

Example	Product
71	3-acetamido-4-methyl-1-N-pyrrolidinocarbonylpyrazole.
72	3-formamido-4-chloro-1-N-p-methylpiperidino(thiocarbonyl)pyrazole.
73	3-propionamido-4-isopropyl-1-N-p-isopropylpiperidinocarbonylpyrazole.
74	3-amino-4-fluoro-1-N-[p-(n-propyl)piperidino]-carbonylpyrazole.
75	3-acetamido-4-ethyl-1-N-phenethylpiperidinocarbonylpyrazole.
76	3-formamido-4-chloro-1-N-(p-diethylaminoethylpiperidino)carbonylpyrazole.
77	3-acetamido-4-bromo-1-N-(p-pyrrolidinoethylpiperidino)-carbonylpyrazole.
78	3-acetamido-4-methyl-1-N-(p-butoxycarbonylpiperidino)-carbonylpyrazole.
79	3-acetamido-4-chloro-1-N-[3,4-di(2-hydroxyethyl)-piperidino]carbonylpyrazole.
80	3-formamido-4-bromo-1-N-o-tolylethylpiperidinocarbonylpyrazole.

The above examples can be repeated to obtain other compounds within the scope of this invention by appropriate selection of reactants as will be readily understood in the art.

The invention claimed is:

1. A compound selected from compounds of the formula



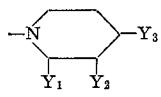
where

X is selected from the group consisting of oxygen and sulfur;

A is selected from the group consisting of

wherein R_1 is methyl; and R_2 is selected from the group consisting of alkyl of 1 through 6 carbons where the alkyl is joined to the carbamyl nitrogen by a carbon selected from the group consisting of a primary and a secondary carbon of said alkyl; alken-2-yl of 3 through 6 carbons where the alken-2-yl is joined to the carbamyl nitrogen by a carbon selected from the group consisting of a primary and a secondary carbon of said alken-2-yl; alkoxyalkyl of 2 through 6 total carbons; dimethylamino; and dialkylaminoalkyl where each of the alkyl groups in the dialkyl portion has 1 through 2 carbons and the remaining alkyl group has 1 through 4 carbons with a total of 3 through 7 in said dialkylaminoalkyl group;

morpholino;
pyrrolidino;
piperidino;
dehydropiperidino;
azabicyclononidino; and
a substituted piperidino group of the structure

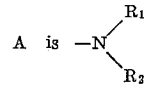


wherein Y_1 is selected from the group consisting of hydrogen and methyl, Y_2 is selected from the group consisting of hydrogen, methyl, ethyl and —$COOR_5$ where R_5 is alkyl of 1 through 4 carbons; and Y_3 is selected from the group consisting of hydrogen, alkyl of 1 through 6 carbons, hydroxyalkyl of 2 through 6 carbons, trifluoromethyl, —$COOR_6$ where R_6 is alkyl of 1 through 4 carbons, dialkylaminoalkyl of 3 through 7 carbons where each of the alkyl groups in the dialkyl portion has 1 through 2 carbons and the remaining alkyl group has 1 through 4 carbons, pyrrolidinomethyl, and hydrocarbon aralkyl of 7 through 9 carbons;

R_3 is selected from the group consisting of hydrogen, formyl, acetyl, propionyl; and

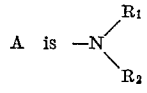
R_4 is selected from the group consisting of hydrogen, chlorine, bromine, fluorine, alkyl of 1 through 3 carbons, and trifluoromethyl.

2. A compound as set forth in claim **1** wherein

A is 

where R_1 is methyl and R_2 is alkyl of 1 through 6 carbons joined to the carbamyl nitrogen by a secondary carbon of the alkyl, R_3 is selected from the group consisting of formyl, acetyl and propionyl, R_4 is chlorine, and X is oxygen.

3. A compound as set forth in claim **1** wherein

A is 

where R_1 is methyl and R_2 is alkyl of 1 through 6 carbons joined to the carbamyl nitrogen by a secondary carbon of the alkyl R_3 is selected from the group consisting of formyl, acetyl and propionyl, R_4 is methyl, and X is oxygen.

4. A compound as set forth in claim **1** wherein A is a heterocyclic group as defined in claim **1**.

5. A compound as set forth in claim **1** wherein A is a 4-mono-substituted piperidino group as defined in claim **1**.

6. A compound as set forth in claim **1** wherein A is piperidino, R_3 is selected from the group consisting of formyl, acetyl and propionyl, R_4 is chlorine, and X is oxygen.

7. A compound as set forth in claim **1** wherein A is piperidino, R_3 is selected from the group consisting of formyl, acetyl and propionyl, R_4 is methyl, and X is oxygen.

8. 1-N-(4 - methylpiperidino)carbonyl-3(5)-formamido-4-chloropyrazole.

9. 1-N-(4-methylpiperidino)carbonyl-3(5)-formamido-4-methylpyrazole.

10. 1-N-(4-methylpiperidino)carbonyl-3(5)-acetamido-4-chloropyrazole.

11. 1-N-(4-methylpiperidino)carbonyl-3(5)-acetamido-4-methylpyrazole.

12. 1 - N-(4-methylpiperidino)carbonyl-3(5)-propionamido-4-chloropyrazole.

13. 1 - N-(4-methylpiperidino)carbonyl-3(5)-propionamido-4-methylpyrazole.

15. 3(5)-acetamido-1-N,N-dimethylcarbamylpyrazole.

14. 1-N,N-dimethylcarbamyl-3(5)-formamidopyrazole.

16. 1-N-methyl-N-isopropylcarbamyl-3(5)-formamidopyrazole.

17. 3(5)-acetamido-1-N-methyl-N-isopropyl-carbamylpyrazole.

18. 1 - N-sec-butyl-N-methylcarbamyl-3(5)-formamidopyrazole.

19. 3(5) - acetamido-1-N-sec-butyl-N-methyl-carbamyl-pyrazole.

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