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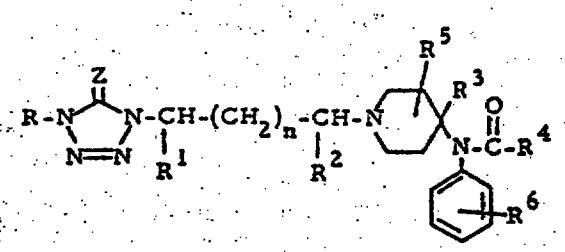

## (54) *N*-PHENYL-*N*-(4-PIPERIDINYL) AMIDES

(71) We, JANNSSEN PHARMACEUTICA N.V., a Belgian Body Corporate, of Naamloze Vennootschap, Turnhoutsebaan 30, Beerse, Belgium, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to *N* - phenyl - *N* - (4 - piperidinyl)amides having a (4,5 - dihydro - 4 - R - 5 - oxo - 1*H* - tetrazol - 1 - yl)alkyl or (4,5 - dihydro-4 - R - thioxo - 1*H* - tetrazol - 1 - yl)alkyl substituent group in the I-position of the piperidine nucleus.

United States Patent No. 3,998,834 describes a number of *N* - phenyl - *N* - (4-piperidinyl)amides having analgesic properties. The compounds of this invention differ from the foregoing essentially by the nature of the (4,5 - dihydro - 4 - R - 5 - oxo-1*H* - tetrazol - I - yl)alkyl or (4,5 - dihydro - 4 - R - 5 - thioxo - I*H* - tetrazol - I-yl)alkyl group present at the I-position of the piperidine nucleus.

The invention provides an *N* - phenyl - *N* - (4 - piperidinyl)amide of the general formula:—



(I)

or a pharmaceutically acceptable acid addition salt thereof, wherein:

R is a hydrogen atom, a lower alkyl, cycloalkyl, lower alkenyl, lower alkynyl, (lower alkyl)-oxy(lower alkyl), aryl or aryl(lower alkyl group;

$R^1$ is a hydrogen atom, a lower alkyl or aryl group;

$R^2$ is a hydrogen atom or a lower alkyl group;

$R^3$ is a lower alkyloxy-carbonyl, lower alkyloxymethyl or lower alkylcarbonyl group;

$R^4$ is a lower alkyl, cycloalkyl, lower alkenyl, lower alkyloxy or arylmethyl group;

$R^5$ is a hydrogen atom or a lower alkyl group;

$R^6$ is a hydrogen atom or halogen atom, or a lower alkyl, lower alkyloxy or trifluoromethyl group;

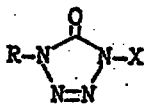
Z is O or S; and

*n* is O or the integer I;

wherein the aryl group as used in the foregoing definitions is a phenyl, substituted phenyl, thienyl or pyridinyl group, the substituted phenyl group having 1 or 2 substituents which are each independently a halogen atom, a lower alkyl, lower alkyloxy or trifluoromethyl group.

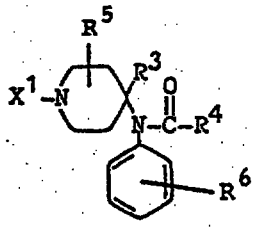
By the term "lower alkyl" as used herein is meant straight and branched chain alkyl radicals having from 1 to 6 carbon atoms, such as, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, butyl, pentyl, and hexyl; by the term "cycloalkyl" is meant cycloalkyl radicals having from 3 to 6 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; by the term "lower alkenyl" is meant alkenyl radicals having from 3 to 6 carbon atoms such as, 2-propenyl, 2-butenyl, 3-pentenyl and 2-hexenyl; by the term "lower alkynyl" is meant alkynyl radicals having from 3 to 6 carbon atoms such as, 2-propynyl and 2-butynyl; and by the term "lower alkyloxy" is meant alkoxy groups containing from 1 to 6 carbon atoms.

The compounds of formula (I) wherein Z is O, (I-a), can generally be prepared by the reaction of a 4,5-dihydro-1*H*-tetrazol-5-one derivative of the formula



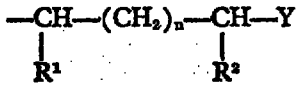
(II)

with a *N*-phenyl-*N*-(4-piperidinyl)amide of the formula



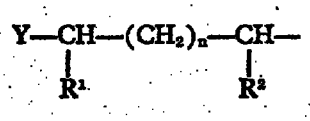
(III)

wherein R, $R^3$, $R^4$, $R^5$ and $R^6$ are as above-defined and either $X^1$ is hydrogen and X is a radical of the formula



(IV)

or X is hydrogen and $X^1$ is a radical of the formula



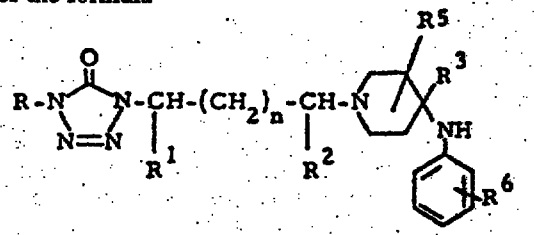
(V)

In the above formulae (IV) and (V) $R^1$, $R^2$ and *n* have the previously indicated meanings and Y is chloro, bromo, iodo, methylsulfonyloxy or 4-methylphenylsulfonyloxy.

The reaction of (II) with (III) may be carried out following standard N-alkylating procedures as generally known in the art. The reaction is advantageously conducted in an appropriate, reaction-inert organic solvent, such as, an aromatic hydrocarbon, e.g. benzene, methylbenzene or dimethylbenzene; a lower alkanol, e.g. methanol, ethanol, 2-propanol or 1-butanol; a ketone, e.g. 4-methyl-2-pentanone; an ether, e.g. 1,4-dioxane or 1,1′ oxybisethane *N*,*N*-dimethylformamide; or nitrobenzene. The addition to the reaction mixture of an appropriate base, such as, an alkali metal carbonate or hydrogen carbonate, or an organic base, such as, *N*,*N*-diethylethanamine or *N*-(1-methylethyl)-2-propanamine may be utilized to pick up the acid that is liberated during the course of the reaction. In some cases the addition of an iodide salt, preferably an alkali metal iodide is appropriate. Somewhat elevated temperatures are advantageously employed to enhance the reaction rate. In some circumstances, especially when one of the substituents $R^1$ and $R^2$ is methyl and the

other is hydrogen, a partial rearrangement may occur during the reaction yielding a mixture of position isomers wherein respectively $R^1$ is methyl and $R^2$ is hydrogen and inversely $R^1$ is hydrogen and $R^2$ is methyl. Such position isomers can easily be separated from each other by known isolation techniques such as, selective crystallisation from an appropriate solvent system or column-chromatography.

The compounds of formula (I-a) can also be prepared by acylating an appropriate 4-piperidinamine of the formula



(VI)

The acylation reaction is conveniently carried out according to known N-acylation procedures, for example, by reacting (VI) with an appropriate acyl halide, $R^4$—CO-halo, representing respectively a lower alkylcarbonyl halide, a cycloalkylcarbonyl halide, an arylacetyl halide or a lower alkyl haloformate, following techniques known in the art. When $R^4$ is a lower alkyl or cycloalkyl group the acylation may also be carried out with an anhydride derived from the acid $R^4COOH$.

The compounds of formula (I) wherein Z is S, (I-b), can generally be derived from the corresponding compounds of the formula (I-a) by reacting the latter with an appropriate sulfurating agent such as, $P_2S_5$. The reaction may be conveniently carried out by stirring and heating the reactants together in an appropriate reaction-inert organic solvent such as, an aromatic hydrocarbon such as, benzene, methylbenzene or dimethylbenzene.

The compounds of formula (I) wherein R represents hydrogen are preferably derived from the corresponding compounds of formula (I) wherein R represents phenylmethyl by debenzylating the latter in the usual manner, e.g. by catalytic hydrogenation using an appropriate catalyst such as palladium-on-charcoal.

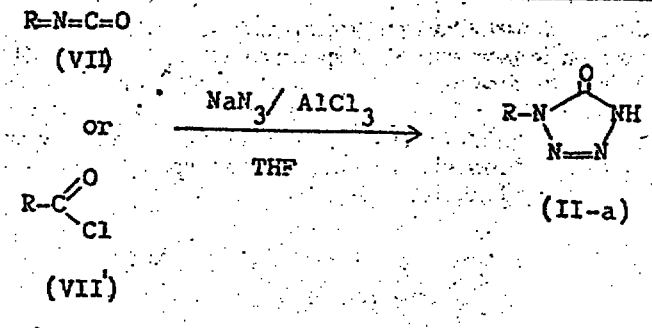
In the foregoing and subsequent preparations, the reaction products are isolated from the reaction mixture, and, if necessary, further purified by the application of common isolation and purification procedures as generally known in the art.

A number of the compounds within the scope of formula (I) have one or more asymmetric carbon atoms within their structure and consequently exist in different stereochemically isomeric forms. More particularly when $R^1$ and $R^2$ are other than hydrogen, the carbon atoms to which they are attached are asymmetric, while additional asymmetric carbon atoms may be present in the lower alkyl groups comprised in R, $R^3$ and $R^4$.

While in the above preparations there are obtained essentially mixtures, including racemic mixtures, of such stereochemical isomers, such mixtures can generally be resolved into their stereochemically pure isomeric forms by the application of known resolution techniques, e.g., by salt formation with optical isomers of asymmetric acids and selective crystallisation of the salts thus obtained. The stereochemically isomeric forms of compounds of formula (I) are included within the scope of formula (I).

As a result of their basic properties, the compounds of formula (I) can be converted to their therapeutically active, non-toxic acid addition salt form by treatment with an appropriate acid, such as, an inorganic acid, such as a hydrohalic acid, e.g. hydrochloric or hydrobromic and sulfuric acid, nitric acid or, phosphoric acid or an organic acid, such as, acetic, propanoic, hydroxyacetic, 2 - hydroxypropanoic, 2 - oxopropanoic, propanedioic, butanedioic, (Z) - 2 - butenedioic, (E) - 2 - butenedioic, 2 - hydroxybutanedioic, 2,3 - dihydroxybutanedioic, 2 - hydroxy - 1,2,3-propanetricarboxylic, benzoic, 3 - phenyl - 2 - propenoic, $\alpha$ - hydroxybenzeneacetic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4 - methylbenzenesulfonic, cyclohexanesulfamic, $\alpha$ - hydroxybenzoic or 4 - amino - 2 - hydroxybenzoic acid. Conversely, the salt form can be converted by treatment with alkali into the free base form.

The starting materials of formula (II) wherein X is hydrogen, (II-a), can easily be prepared by the reaction of an appropriate isocyanate of the formula (VII') or an acyl chloride of the formula (VII) with sodium azide in the presence of aluminium chloride in an appropriate organic solvent, preferably an ether such as tetrahydrofuran (THF).

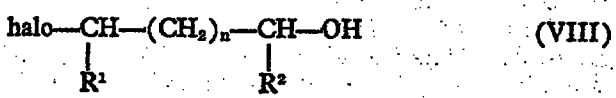


The reaction is conveniently carried out by stirring and heating the reactants together in the solvent for several hours. When an acyl chloride of formula (VII') is used as a reactant at least 2 molar equivalents of the azide have to be employed and the use of an additional excess thereof is generally found appropriate.

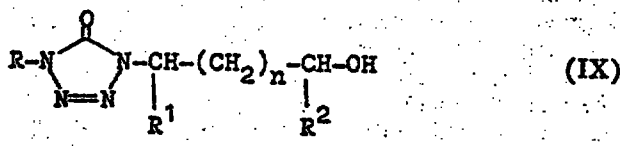
Starting materials of formula (II) wherein X is a radical of the formula (IV), (II-b), can be obtained by introducing said radical into the corresponding (II-a) by known methods.

In general, said starting materials (II-b) can be prepared by carrying out the steps of:

i) reacting the appropriate (II-a) with a haloalkanol derivative of the formula

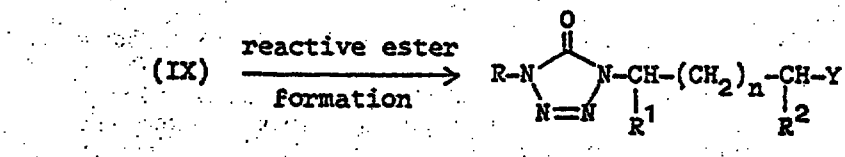


following generally known N-alkylating procedures as previously described herein, to obtain an intermediate of the formula



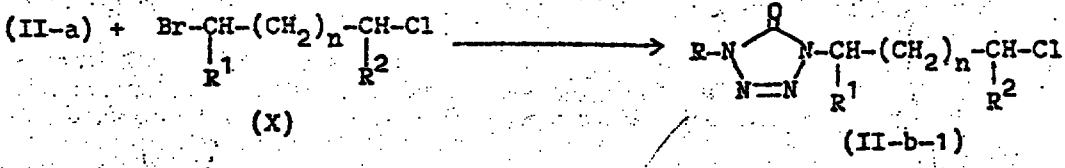
and;

ii) subsequently converting the hydroxy group of the thus obtained (IX) into the group Y as above defined following art-known procedures of preparing reactive esters starting from the corresponding alcohols.

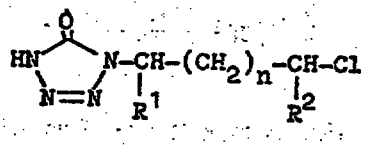


Halides are conveniently obtained by the reaction of (IX) with an appropriate halogenating agent, such as, sulfinyl chloride, sulfuryl chloride, phosphor pentachloride, phosphor pentabromide or phosphoryl chloride. When the group Y is an iodide, it is preferably derived from the corresponding chloride or bromide by the replacement of that halogen with iodine. Methanesulfonates and 4-methylbenzenesulfonates are conveniently prepared by reacting the alcohol with an appropriate sulfonyl halide such as, methanesulfonyl chloride and 4-methylbenzenesulfonyl chloride respectively.

When Y is (II-b) is chloro, (II-b-1), the introduction of the chloroalkyl chain can also be performed by the reaction of an appropriate (II-a) with an appropriate bromo-chloroalkane derivative of the formula (X) following standard N-alkylating procedures to obtain the corresponding (II-b-1).



Alternatively, the starting material (II-b-1) wherein R is other than hydrogen or phenyl can be obtained by introducing the R-substituent into a precursor of the formula

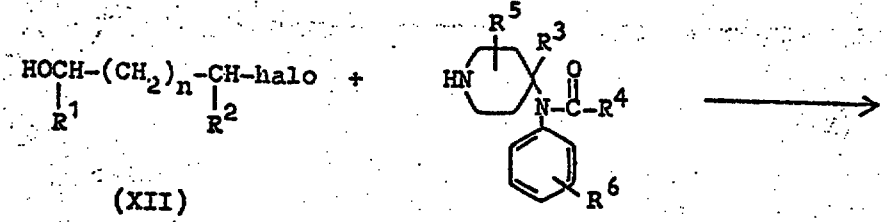


(XI)

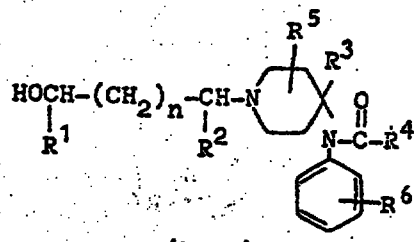
Said introduction of R is conveniently carried out by the reaction of (XI) with an appropriate reactive ester RY wherein R is as previously defined but other than hydrogen or phenyl, following standard N-alkylating procedures as described hereinabove. It is to be noted that when said Y in said RY is iodo, the chloro substituent of (XI) may be replaced during the reaction by iodo, especially when an excess of the alkylating iodide is employed. The precursor compounds of formula (XI) may be prepared following the procedures described in Tetrahedron, *31*, 765 (1975) wherein the compound of formula (XI) wherein $R^1$ and $R^2$ are both hydrogen and n is 1 is specifically described.

The starting materials of formula (III) wherein $X^1$ is hydrogen, (III-a), can be prepared according to the procedures outlined in U.S. Pat. No. 3,998,834 wherein a number of such starting materials and their preparation are described.

The starting materials of formula (III) wherein $X^1$ is a radical of the formula (V), (III-b), can be prepared by N-alkylating a piperidine derivative of the formula (III-a) with a haloalkanol of the formula (XII) in the usual manner to obtain an intermediate of the formula (XIII) and thereafter converting the hydroxy group of the latter into a reactive ester group as previously described.

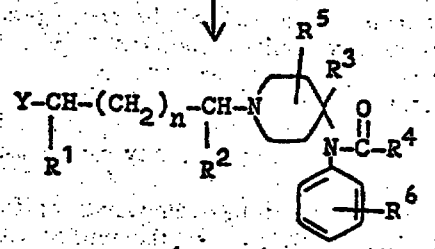


(XII) (III-a)



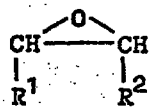
(XIII)

reactive ester formation



(III-b)

Intermediates of formula (XIII) herein wherein n is 0 can also be obtained by the reaction of (III-a) with an appropriately substituted oxirane of the formula

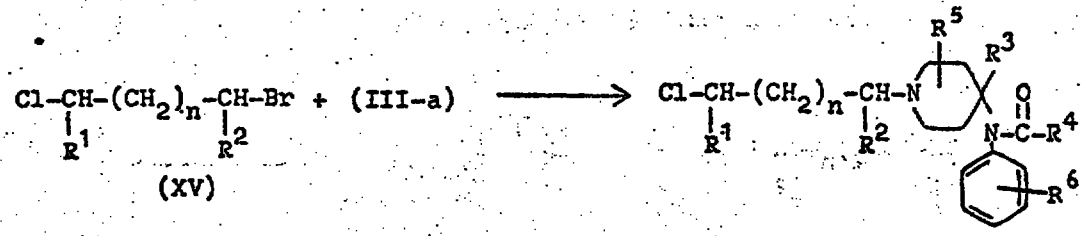


(XIV)

It is to be noted that when in formula (XIV) one of the radicals $R^1$ and $R^2$ is methyl, the other being hydrogen, there is substantially obtained an intermediate (XIII) wherein the methyl substituent is located at the $\beta$-position with respect to the piperidine nitrogen. Intermediates of formula (XIII) wherein $R^1$ is phenyl and n is zero and methods of preparing them are also described in United States Patent No. 3,998,834.

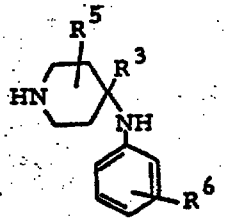
The reaction of (XIV) with (III-a) is conveniently carried out by stirring and heating the reactants together in an appropriate organic solvent, such as, an aromatic hydrocarbon, e.g., benzene, methylbenzenze, or dimethylbenzene, a halogenated hydrocarbon, e.g., dichloromethane and trichloromethane; or a lower alkanol, e.g., methanol, ethanol or 2-propanol and preferably in a mixture of an aromatic hydrocarbon and a lower alkanol. The reaction may be promoted by the addition of an appropriate base, such as, an alkali metal carbonate or hydrogen carbonate.

Starting materials of formula (III-b) wherein Y is chloro, (III-b-1), can also be prepared directly by the reaction of (III-a) with a bromo-chloroalkane of the formula (XV) following methods similar to those described herein for the preparation of starting materials (II-b-1) starting from (II-a).



(XV) (III-b-1)

The starting materials of formula (VI) herein can generally be prepared by the reaction of a reactive ester of the formula (II) wherein X represents a radical of the formula (IV) with a 4-piperidinamine of the formula



(XVI)

following similar procedures as described herein for the preparation of the compounds (I-a) starting from (II) and (III).

The 4-piperidinamines of formula (XVI) used as starting materials herein can also be prepared following the procedures described in U.S. Pat. No. 3,998,834 wherein a number of such compounds are specifically described.

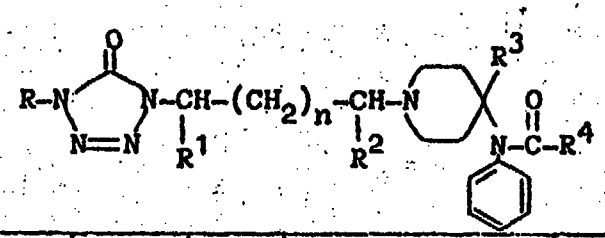
The ultimate starting materials in each of the above procedures are generally known and they may all be prepared following art-known procedures as are described in the literature for preparing such known compounds.

The compounds of formula (I) and the pharmaceutically acceptable acid addition salts thereof have very interesting pharmacological properties. More particularly they are potent morphine-like analgesics and as such they can be used to depress pain in warm-blooded animals.

The useful analgesic properties of the compounds of formula (I) and acid addition salts thereof are clearly evidenced by the results obtained in the rat tail withdrawal test, described in Arzneimittel-Forschung, *13*, 502 (1963 and *21*, 862 (1971).

The results in the table I below indicate the LED, i.e. the lowest 100% effective dose in mg/kg upon intravenous administration, and the duration (expressed in minutes) of this effect at the stated dose.

Table I



| R | $CH-(CH_2)_n-CH$ ($R^1$, $R^2$) | $R^3$ | $R^4$ | Base or Salt form | LED in mg/kg s.c. | duration in min. |
|---|---|---|---|---|---|---|
| $CH_3$ | $CH_2-CH_2$ | $COOCH_3$ | $C_2H_5$ | $(COOH)_2$ | 0.16 | 39 |
| $C_2H_5$ | $CH_2-CH_2$ | $COOCH_3$ | $C_2H_5$ | $11/2(COOH)_2$ | 0.16 | 19 |
| $nC_3H_7$ | $CH_2-CH_2$ | $COOCH_3$ | $C_2H_5$ | $(COOH)_2$ | 0.16 | 11 |
| $iC_3H_7$ | $CH_2-CH_2$ | $COOCH_3$ | $C_2H_5$ | $(COOH)_2$ | 2.5 | 41 |
| $tC_4H_9$ | $CH_2-CH_2$ | $COOCH_3$ | $C_2H_5$ | $(COOH)_2$ | 2.5 | 18 |
| $nC_5H_{11}$ | $CH_2-CH_2$ | $COOCH_3$ | $C_2H_5$ | $(COOH)_2$ | 2.5 | 20 |
|  | $CH_2-CH_2$ | $COOCH_3$ | $C_2H_5$ | $(COOH)_2$ | <0.63 | 150 |
|  | $CH_2-CH_2$ | $COOCH_3$ | $C_2H_5$ | $(COOH)_2$ | >10 | 45 |
| $CH_3$ | $CH_2-CH_2$ | $CH_2OCH_3$ | $C_2H_5$ | $(COOH)_2$ | 0.16 | 31 |
| $C_2H_5$ | $CH_2-CH_2$ | $CH_2OCH_3$ | $C_2H_5$ | $HCl.H_2O$ | 0.08 | 17 |
| $iC_3H_7$ | $CH_2-CH_2$ | $CH_2OCH_3$ | $C_2H_5$ | $HNO_3.H_2O$ | 0.63 | 12 |
| $C_2H_5$ | $CH_2-CH(CH_3)$ | $CH_2OCH_3$ | $C_2H_5$ | $HNO_3$ | 0,16 | 13 |
| $C_6H_5$ | $CH_2-CH(CH_3)$ | $CH_2OCH_3$ | $C_2H_5$ | $HNO_3$ | 10 | 14 |
| $C_2H_5$ | $CH_2-CH_2-CH_2$ | $CH_2OCH_3$ | $C_2H_5$ | $HCl1/2H_2O$ | 2.5 | 14 |

A preferred group of compounds within the scope of formula (I) is represented by those wherein R is a lower alkyl radical. In fact these preferred compounds are highly potent analgesics having a short duration of action. Analgesics having such a short duration of action are highly desirable in circumstances where acute severe pain has to be eliminated over a short period, e.g., in anaesthesiology.

In view of their analgesic activity, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, an effective analgesic amount of the particular compound, in base or acid-addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, water, glycols, oil or alcohols in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders and disintegrating agents in the case of powders, pills, capsules and tablets. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers or suspending agents may be employed. Acid addition salts of (I), due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonsful or tablespoonsful and segregated multiples thereof.

In view of the analgesic activity of the subject compounds, it is evident that the compounds of the present invention can be used in preventing or combatting pain in warm-blooded animals, by the systemic administration of an effective analgesic amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutical carrier.

Although the amount of active ingredient to be administered may vary within rather wide limits, depending on the particular circumstances of the case, doses of from 0.01 mg/kg to 1 mg/kg, administered once or repeatedly are generally found effective.

The following Examples are intended to illustrate and not to limit the scope of the present invention. Unless otherwise stated all parts therein are by weight. Examples I to X describe the preparation of intermediate derivatives.

## EXAMPLE I.

To a stirred mixture of 14.2 parts of ethyl isocyanate, 29.2 parts of sodium azide and 135 parts of dry tetrahydrofuran is added a solution of 39 parts of aluminium chloride in 225 parts of dry tetrahydrofuran. Stirring is continued overnight at reflux temperature. The reaction mixture is cooled and acidified with a hydrochloric acid solution 6N. The whole is evaporated to dry and the product is extracted four times with 2-propanone. The combined extracts are dried, filtered and evaporated. The residue is dried overnight, yielding 18 parts (65%) of 1 - ethyl - 1,4 - dihydro - 5*H*-tetrazol - 5 - one.

## EXAMPLE II.

Following the procedure of Example I and using an equivalent amount of respectively cyclohexyl isocyanate and isopropyl isocyanate as a starting material there are obtained:

1 - cyclohexyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one; and
1,4 - dihydro - 1 - (1 - methylethyl) - 5*H* - tetrazol - 5 - one as a residue.

## EXAMPLE III.

To 990 parts of tetrahydrofuran, cooled in an ice-bath, are added portionwise 156 parts of aluminium chloride and the whole is stirred vigorously till all solid enters solution. This solution is added quickly to a stirred suspension of 208 parts of sodium azide in 225 parts of tetrahydrofuran and stirring is continued for 1 hour at reflux temperature. After cooling to room temperature, there is added dropwise a solution of 54 parts of butanoyl chloride in 225 parts of tetrahydrofuran at a temperature below 30°C. The whole is heated slowly to reflux and stirring is continued overnight at reflux temperature. While cooling, the reaction mixture is acidified with 800 parts of a hydrochloric acid solution 6N and the solvent is evaporated. The residue is stirred in a sodium hydrogen carbonate solution, trichloromethane is added and the layers are separated. The aqueous phase is acidified with concentrated hydrochloric acid and the solvent is evaporated: The residue is stirred in 2-propanone. The precipitate is filtered off and the filtrate is evaporated, yielding 32 parts of 1,4-dihydro - 1 - propyl - 5*H* - tetrazol - 5 - one as a residue.

## EXAMPLE IV.

Following the procedure of Example III and using an equivalent amount of an appropriate acyl chloride as a starting material, the following compounds are obtained:
1 - (1,1 - dimethylethyl) - 1,4 - dihydro - 5*H* - tetrazol - 5 - one as a residue;
1,4 - dihydro - 1 - pentyl - 5*H* - tetrazol - 5 - one;
1,4 - dihydro - 1 - (2 - phenylethyl) - 5*H* - tetrazol - 5 - one as a solid residue;
1,4 - dihydro - 1 - (phenylmethyl) - 5*H* - tetrazol - 5 - one; mp. 152°C; and
1 - cyclopropyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one; mp. 128°C.

## EXAMPLE V.

A mixture of 22 parts of 1 - ethyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one, 45 parts of 1 - bromo - 2 - chloroethane, 26 parts of sodium carbonate, 0.3 parts of potassium iodide and 240 parts of 4 - methyl - 2 - pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled, water is added and the layers are separated. The aqueous phase is extracted three times with dichloromethane. The combined organic phases are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using trichloromethane as eluent. The pure fractions are collected and the eluent is evaporated, yielding 28.4 parts (80%) of 1 - (2 - chloroethyl) - 4 - ethyl - 1,4 - dihydro - 5*H* - tetrazol - 5-one as a residue.

## EXAMPLE VI.

Following the procedure of Example V and using equivalent amounts of respectively an appropriate 1,4 - dihydro - 5*H* - tetrazol - 5 - one and an appropriate bromochloroalkane as starting materials the following 1 - (chloroalkyl) - 1,4 - dihydro - 5*H*-tetrazol - 5 - ones are obtained:

1 - (2 - chloroethyl) - 1,4 - dihydro - 4 - propyl - 5*H* - tetrazol - 5 - one as a residue;
1 - (2 - chloroethyl) - 1,4 - dihydro - 4 - (1 - methylethyl) - 5*H* - tetrazol - 5-one as a residue;
1 - (2 - chloroethyl) - 4 - (1,1 - dimethylethyl) - 1,4 - dihydro - 5*H* - tetrazol-5 - one as a residue;
1 - (2 - chloroethyl) - 1,4 - dihydro - 4 - pentyl - 5*H* - tetrazol - 5 - one as a residue;
1 - (2 - chloroethyl) - 4 - cyclohexyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one as a residue;
1 - ( 2 - chloroethyl) - 1,4 - dihydro - 4 - (2 - phenylethyl) - 5*H* - tetrazol - 5 - one as a residue; and
1 - (3 - chloropropyl) - 4 - ethyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one as a residue;

1 - (2 - chloroethyl) - 1,4 - dihydro - 4 - (phenylmethyl) - 5*H* - tetrazol - 5 - one as a residue and;
1 - (2 - chloroethyl) - 4 - cyclopropyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one as a residue.

## EXAMPLE VII.

A mixture of 49 parts of iodomethane, 10.5 parts of 1 - (2 - chloroethyl) - 1,4-dihydro - 5*H* - tetrazol - 5 - one, 15 parts of sodium carbonate, 0.2 parts of potassium iodide and 240 parts of 4 - methyl - 2 - pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled, 100 parts of water are added and the layers are separated. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using trichloromethane as eluent. The pure fractions are collected and the eluent is evaporated, yielding 15 parts (85%) of 1,4 - dihydro - 1 - (2 - iodoethyl) - 4 - methyl - 5*H* - tetrazol - 5 - one as a residue.

## EXAMPLE VIII.

A mixture of 19.6 parts of [2 - (2 - thienyl)ethyl] - 4 - methylbenzenesulfonate, 10 parts of 1 - (2 - chloroethyl) - 1,4 - dihydro - 5*H* - tetrazol - 5 - one, 10 parts of sodium carbonate and 90 parts of *N*,*N*-dimethylformamide is stirred and heated overnight at 70°C. The reaction mixture is cooled, 100 parts of water are added and the product is extracted three times with methylbenzene. The combined extracts are dried, filtered and evaporated. The residue is purifid by column-chromatography over silica gel using a mixture of trichloromethane and petroleum ether (70:30 by volume) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 15 parts (46.5%) of 1 - (2 - chloroethyl) - 1,4 - dihydro - 4 - [2 - (2 - thienyl)ethyl] - 5*H* - tetrazol - 5 - one as a residue.

## EXAMPLE IX.

To 4.5 parts of sulfinyl chloride is added dropwise a mixture of 13 parts of *N*-[1 - (2 - hydroxy - 2 - phenylethyl) - 4 - (methoxymethyl) - 4 - piperidinyl] - *N*-phenylpropanamide hydrochloride and 260 parts of dichloromethane. Upon completion, the whole is stirred and refluxed for a few hours. The reaction mixture is cooled and the solvent is evaporated. The residue is taken up in 2-propanone. The mixture is filtered and the filtrate is treated with activated charcoal. The latter is filtered off and the filtrate is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane. The product is filtered off and dried, yielding 9.2 parts (61.7%) of *N* - [1 - (2 - chloro - 2 - phenylethyl) - 4 - methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide monohydrochloride; mp. 145.3°C.

## EXAMPLE X.

A mixture of 35 parts of 2-methyloxirane, 83 parts of *N* - [4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide, 25 parts of sodium hydrogen carbonate, 450 parts of benzene and 80 parts of methanol is stirred and refluxed overnight. The reaction mixture is evaporated and the residue is taken up in water. The product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanol. The salt is filtered off and crystallized from a mixture of 2,2'-oxybispropane and 2-propanol, yielding 41.5 parts (37%) of *N* - [1 - (2 - hydroxypropyl) - 4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide monohydrochloride.

14 Parts of sulfinyl chloride are stirred and there is added dropwise a solution of 37 parts of *N* - [1 - (2 - hydroxypropyl) - 4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide monohydrochloride in 360 parts of dichloromethane. Upon completion, stirring is continued overnight at reflux temperature. The reaction mixture is evaporated and the residue is suspended in 2-propanone. The product is filtered off and dried, yielding 31.5 parts (85%) of *N* - [1 - (2 - chloropropyl) - 4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide monohydrochloride.

## EXAMPLE XI.

A mixture of 1.8 parts of 1 - (2 - chloroethyl) - 4 - ethyl - 1,4 - dihydro - 5*H*-tetrazol - 5 - one, 3.45 parts of *N* - [4 - (methoxymethyl) - 4 - piperidinyl] - *N*-phenylpropanamide, 5 parts of sodium carbonate, 0.2 parts of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by

column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and crystallized from 2-propanone, yielding 1.5 parts (33.3%) of *N* - {1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1 - yl]ethyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide monohydrochloride monohydrate; m.p. 140.8°C.

## EXAMPLE XII.

Following the procedure of Example XI and using equivalent amounts of the appropriate starting materials, the following compounds are obtained as acid addition salts after treatment of the free base form with an appropriate acid:

*N* - {1 - [2 - (4,5 - dihydro - 5 - oxo - 4 - propyl - 1*H* - tetrazol - 1 - yl)ethyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide ethanedioate (1:2) monohydrate; mp. 103.8°C.

*N* - [1 - {2 - [4,5 - dihydro - (1 - methylethyl) - 5 - oxo - 1*H* - tetrazol - 1 - yl] - ethyl} - 4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide mononitrate monohydrate; mp. 104.5°C;

methyl 1 - [2 - {4,5 - dihydro - 5 oxo - 4 - [2 - (2 - thienyl)ethyl] - 1*H*-tetrazol - 1 - yl}ethyl] - 4 - [(*N* - 1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (1:1) mp. 162.9°C;

*N* - {1 - [3 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1 - yl)propyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide hydrochloride hemihydrate; mp. 182°C; and

*N* - [1 - {2 - [4,5 - dihydro - 5 - oxo - 4 - (phenylmethyl) - 1*H* - tetrazol-1 - yl]ethyl} - 4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide ethanedioate (1:1); mp. 166.4°C.

## EXAMPLE XIII.

A mixture of 3.6 parts of 1 - (2 - chloroethyl) - 4 - ethyl - 1,4 - dihydro - 5*H*-tetrazol - 5 - one, 6.4 parts of methyl 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate hydrochloride, 4 parts of sodium carbonate, 0.1 parts of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled and poured onto water. The organic phase is separated, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the ethanedioate salt in 2-propanone. The salt is filtered off and dried, yielding 1.5 parts (13%) of methyl 1 - [2 - (4-ethyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1 - yl)ethyl] - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (2:3); mp. 158.9°C.

## EXAMPLE XIV.

Following the procedure of Example XIII and using equivalent amounts of the appropriate starting materials, the following ethanedioate salts are obtained:

methyl 1 - [2 - (4,5 - dihydro - 5 - oxo - 4 - propyl - 1*H* - tetrazol - 1 - yl)-ethyl] - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (1:1); mp. 168.4°C;

methyl 1 - {2 - [4,5 - dihydro - 4 - (1 - methylethyl) - 5 - oxo - 1*H* - tetrazol-1 - yl]ethyl} - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (1:1); mp. 184.2°C;

methyl 1 - {2 - [4 - (1,1 - dimethylethyl) - 4,5 - dihydro - 5 - oxo - 1*H*-tetrazol - 1 - yl]ethyl} - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (1:1); mp. 168.1°C;

methyl 1 - [2 - (4,5 - dihydro - 5 - oxo - 4 - pentyl - 1*H* - tetrazol - 1 - yl)-ethyl] - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (1:3); mp. 153.5°C;

methyl 1 - [2 - (4 - cyclohexyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1 - yl)-ethyl] - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (1:1); mp. 173°C;

methyl 1 - {2 - [4,5 - dihydro - 5 - oxo - 4 - (2 - phenylethyl) - 1*H* - tetrazol-1 - yl]ethyl} - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (2:3); mp. 162.2°C;

methyl 1 - {2 - [4,5 - dihydro - 5 - oxo - 4 - (phenylmethyl) - 1*H* - tetrazol-1 - yl]ethyl} - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (1:1); mp. 191.7°C;

methyl 1 - [2 - (4 - cyclopropyl) - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1-yl)ethyl] - 4 - [(*N* - 1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (2:3 hemihydrate; mp. 155.9°C; and

methyl 1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1 - yl)ethyl] - 4 - (phenylamino) - 4 - piperidinecarboxylate ethanedioate (2:3); mp. 172°C.

## EXAMPLE XV.

A mixture of 2.55 parts of 1,4 - dihydro - 1 - (2 - iodoethyl) - 4 - methyl - 5*H*-tetrazol - 5 - one, 3.45 parts of *N* - [4 - (methoxymethyl) - 4 - piperidinyl] - *N*-phenylpropanamide, 2 parts of sodium carbonate, 0.2 parts of potassium iodide and 160 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled, 100 parts of water are added and the layers are separated. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the ethanedioate salt in 2-propanone. The salt is filtered off and crystallized from 2-propanone, yielding 2.1 parts 42%) of *N*-{1 - [2 - (4,5 - dihydro - 4 - methyl - 5 - oxo - 1*H* - tetrazol - 1 - yl)ethyl] - 4-(methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide ethanedioate (1:1); mp. 155.9°C.

## EXAMPLE XVI.

Following the procedure of Example XV there is prepared methyl 1 - [2 - 4,5-dihydro - 4 - methyl - 5 - oxo - 1*H* - tetrazol - 1 - yl)ethyl] - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate ethanedioate (1:1); mp. 185.9°C; by the reaction of 1,4 - dihydro - 1 - (2 - iodoethyl) - 4 - methyl - 5*H*-tetrazol - 5 - one with methyl 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4-piperidinecarboxylate.

## EXAMPLE XVII.

A mixture of 3 parts of 1 - ethyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one, 9.4 parts of N - [1 - (2 - chloropropyl) - 4 - (methoxymethyl) - 4 - piperidinyl] - *N*-phenylpropanamide, 2.5 parts of sodium carbonate, 2.5 parts of *N*,*N*-diethylethanamine and 90 parts of *N*,*N*-dimethylformamide is stirred and heated overnight at 70°C. The reaction mixture is cooled, 100 parts of water are added and the product is extracted three times with methylbenzene. The combined extracts are dried, filtered and evaporated. The residue is purified twice by column-chromatography over silica gel using first a mixture of trichloromethane and methanol (97:3 by volume) and then a mixture of ethyl acetate and ethanol (99:1 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone and 2,2'-oxybispropane. The salt is filtered off and dried, yielding 2.1 parts (18%) of *N* - {1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H*-tetrazol - 1 - yl) - 1 - methylethyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N*-phenylpropanamide monohydrochloride; mp. 185.4°C.

## EXAMPLE XVIII.

A mixture of 1.2 parts of 1 - ethyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one, 3.9 parts of *N* - [1 - (2 - chloropropyl) - 4 - (methoxymethyl) - 4 - piperidinyl] - *N*-phenylpropanamide monohydrochloride, 2 parts of sodium carbonate, 0.1 parts of potassium iodide and 120 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled, poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (99:1 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the nitrate salt in 2-propanone. The salt is filtered off and crystallized twice; first from a mixture of 2,2'-oxybispropane and 2-propanone and then from 2-propanone, yielding 1.5 parts (30%) of *N* - {1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1-yl) - 1 - methylethyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide mononitrate; mp. 146.6°C.

## EXAMPLE XIX.

Following the procedure of Example XVIII there is prepared *N* - {1 - [2 - (4,5-dihydro - 5 - oxo - 4 - phenyl - 1*H* - tetrazol - 1 - yl) - 1 - methylethyl] - 4-(methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide mononitrate; mp. 151.2°C; by the reaction of 1,4 - dihydro - 1 - phenyl - 5*H* - tetrazol - 5 - one with *N* - [1 - (2 - chloropropyl) - 4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide monohydrochloride.

## EXAMPLE XX.

A mixture of 3 parts of 1 - ethyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one, 8 parts of *N* - [1 - (2 - chloro - 2 - phenylethyl) - 4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide, 0.2 parts of potassium iodide, 5 parts of sodium carbonate and 135 parts of *N*,*N*-dimethylformamide is stirred and heated overnight at 70°C. The reaction mixture is cooled to room temperature and 150 parts of water are added. The product is extracted three times with methylbenzene. The combined extracts are dried, filtered and evaporated. The solid residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of petroleumether and 2,2'-oxybispropane. The product is filtered off and dried, yielding 5.7 parts (65%) of *N* - {1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1 - yl) - 2-phenylethyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide; mp. 125.7°C.

## EXAMPLE XXI.

A mixture of 3 parts of 1 - ethyl - 1,4 - dihydro - 5*H* - tetrazol - 5 - one, 9.4 parts of *N* - [1 - (2 - chloropropyl) - 4 - (methoxymethyl) - 4 - piperidinyl] - *N*-phenylpropanamide monohydrochloride, 2.5 parts of *N*,*N*-diethylethanamine, 2.5 parts of sodium carbonate and 90 parts of *N*,*N*-dimethylformamide is stirred and heated overnight at 70°C. The reaction mixture is cooled and 100 parts of water are added. The product is extracted three times with methylbenzene. The combined extracts are dried, filtered and evaporated. The residue is purified twice by column-chromatography over silica gel using first a mixture of trichloromethane and methanol (97:3 by volume) and then a mixture of ethyl acetate and ethanol (99:1 by volume), as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone and 2,2'-oxybispropane. The salt is filtered off and dried, yielding 3.9 parts (33.4%) of *N* - {1 - [2 - (4 - ethyl - 4,5 - dihydro-5 - oxo - 1*H* - tetrazol - 1 - yl]propyl] - 4 - (methoxymethyl) - 4 - piperidinyl}-*N* - phenylpropanamide monohydrochloride; mp. 192.7°C.

## EXAMPLE XXII.

A mixture of 5.7 parts of methyl 1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H*-tetrazol - 1 - yl)ethyl] - 4 - (phenylamino) - 4 - piperidinecarboxylate, 1.9 parts of cyclopropanecarbonyl chloride, 2.7 parts of *N*,*N*-diethylethanamine and 68 parts of methylbenzene is stirred and refluxed overnight. The reaction mixture is cooled, 100 parts of water are added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and treated with 1 part of ethanedioic acid. The formed ethanedioate salt is filtered off and crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 1.5 parts (17.5%) of methyl 4 - [*N* - (cyclopropylcarbonyl) - *N* - phenylamino] - 1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H*-tetrazol - 1 - yl)ethyl] - 4 - piperidinecarboxylate ethanedioate (2:3); mp. 181.5°C.

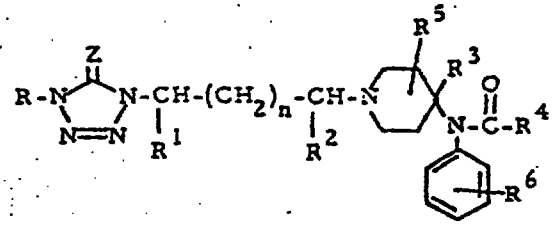
## EXAMPLE XXIII.

Following the procedures described herein and using appropriate starting materials the following compounds of formula I can still be prepared:

| R | Z | n | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|---|---|
| H | O | 0 | H | H | $COOCH_3$ | $C_2H_5$ | H | H |
| H | S | 1 | H | H | $COOCH_3$ | $C_2H_5$ | H | H |
| H | O | 0 | H | H | $CH_2OCH_3$ | $CH_3$ | 3-$CH_3$ | H |
|  | O | 0 | H | H | $COOC_2H_5$ | $C_2H_5$ | H | H |
| $CH_2$=CH–$CH_2$ | O | 0 | H | H | $COOC_2H_5$ | $C_2H_5$ | H | H |
| $CH_2$=CH–$CH_2$ | O | 0 | H | H | $COCH_3$ | $C_2H_5$ | H | H |
| CH≡C–$CH_2$ | O | 0 | H | H | $COOC_2H_5$ | $C_2H_5$ | H | H |
| $C_2H_5O$–$CH_2CH_2$ | O | 0 | H | H | $COOC_2H_5$ | $C_2H_5$ | H | H |
| 4-Cl-$C_6H_4$ | O | 0 | H | H | $COCH_3$ | $C_2H_5$ | H | H |
| 2-F-$C_6H_4$ | O | 0 | H | H | $COCH_3$ | $C_2H_5$ | 3-$CH_3$ | 4-Cl |
| 4-$CH_3$-$C_6H_4$ | O | 0 | H | H | $COOCH_3$ | $C_3H_7$ | H | 4-Cl |
| 2,4-$(CH_3O)_2$-$C_6H_3$ | O | 0 | H | H | $CH_2OCH_3$ | $C_2H_5$ | H | 4-F |
| 3-$(CF_3)$-$C_6H_4$ | O | 0 | H | H | $COOC_2H_5$ | $CH_3$ | 3-$CH_3$ | 3-$CF_3$ |
| 4-Cl-$C_6H_4$-$CH_2$ | O | 0 | H | H | $COOCH_3$ |  | H | H |
| 2-(2-thienyl)ethyl | O | 0 | H | H | $COOCH_3$ | $CH_2$–CH=$CH_2$ | H | H |
| 2-(2-pyridinyl)ethyl | O | 0 | H | H | $COCH_3$ | $OC_2H_5$ | H | 4-$CH_3$ |
| $C_2H_5$ | S | 1 | H | H | $COOCH_3$ | $CH_2$-$C_6H_5$ | H | 4-$OCH_3$ |

WHAT WE CLAIM IS:—

1. An *N*-phenyl-*N*-(4-piperidinyl)amide derivative having the general formula:—



wherein:

R is a hydrogen atom, a lower alkyl, cycloalkyl, lower alkenyl, lower alkynyl, (lower alkyl)oxy(lower alkyl), aryl or aryl(lower alkyl group;

$R^1$ is a hydrogen atom, a lower alkyl or aryl group;

$R^2$ is a hydrogen atom or a lower alkyl group;

$R^3$ is a lower alkyloxy-carbonyl, lower alkyloxymethyl or lower alkylcarbonyl group;

$R^4$ is a lower alkyl, cycloalkyl, lower alkenyl, lower alkyloxy or arylmethyl group;

$R^5$ is a hydrogen atom or a lower alkyl group;

$R^6$ is a hydrogen or halogen atom, or a lower alkyl, lower alkyloxy or trifluoromethyl group;

Z is O or S; and

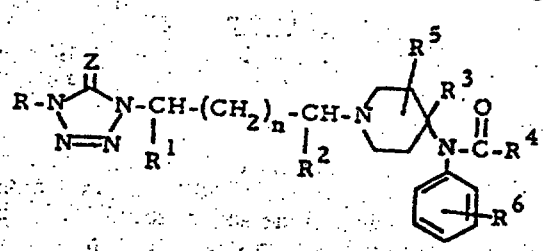
*n* is O or the integer 1;

wherein the aryl group as used in the foregoing definitions is a phenyl, substituted phenyl, thienyl or pyridinyl group, the substituted phenyl group having 1 or 2 sub-

| R | Z | n | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|---|---|
| H | O | 0 | H | H | $COOCH_3$ | $C_2H_5$ | H | H |
| H | S | 1 | H | H | $COOCH_3$ | $C_2H_5$ | H | H |
| H | O | 0 | H | H | $CH_2OCH_3$ | $CH_3$ | 3-$CH_3$ | H |
|  | O | 0 | H | H | $COOC_2H_5$ | $C_2H_5$ | H | H |
| $CH_2$=CH–$CH_2$ | O | 0 | H | H | $COOC_2H_5$ | $C_2H_5$ | H | H |
| $CH_2$=CH–$CH_2$ | O | 0 | H | H | $COCH_3$ | $C_2H_5$ | H | H |
| CH≡C–$CH_2$ | O | 0 | H | H | $COOC_2H_5$ | $C_2H_5$ | H | H |
| $C_2H_5O$–$CH_2CH_2$ | O | 0 | H | H | $COOC_2H_5$ | $C_2H_5$ | H | H |
| 4-Cl-$C_6H_4$ | O | 0 | H | H | $COCH_3$ | $C_2H_5$ | H | H |
| 2-F-$C_6H_4$ | O | 0 | H | H | $COCH_3$ | $C_2H_5$ | 3-$CH_3$ | 4-Cl |
| 4-$CH_3$-$C_6H_4$ | O | 0 | H | H | $COOCH_3$ | $C_3H_7$ | H | 4-Cl |
| 2,4-$(CH_3O)_2$-$C_6H_3$ | O | 0 | H | H | $CH_2OCH_3$ | $C_2H_5$ | H | 4-F |
| 3-$(CF_3)$-$C_6H_4$ | O | 0 | H | H | $COOC_2H_5$ | $CH_3$ | 3-$CH_3$ | 3-$CF_3$ |
| 4-Cl-$C_6H_4$-$CH_2$ | O | 0 | H | H | $COOCH_3$ |  | H | H |
| 2-(2-thienyl)ethyl | O | 0 | H | H | $COOCH_3$ | $CH_2$–CH=$CH_2$ | H | H |
| 2-(2-pyridinyl)ethyl | O | 0 | H | H | $COCH_3$ | $OC_2H_5$ | H | 4-$CH_3$ |
| $C_2H_5$ | S | 1 | H | H | $COOCH_3$ | $CH_2$-$C_6H_5$ | H | 4-$OCH_3$ |

WHAT WE CLAIM IS:—

1. An *N*-phenyl-*N*-(4-piperidinyl)amide derivative having the general formula:—



wherein:

R is a hydrogen atom, a lower alkyl, cycloalkyl, lower alkenyl, lower alkynyl, (lower alkyl)oxy(lower alkyl), aryl or aryl(lower alkyl group;

$R^1$ is a hydrogen atom, a lower alkyl or aryl group;

$R^2$ is a hydrogen atom or a lower alkyl group;

$R^3$ is a lower alkyloxy-carbonyl, lower alkyloxymethyl or lower alkylcarbonyl group;

$R^4$ is a lower alkyl, cycloalkyl, lower alkenyl, lower alkyloxy or arylmethyl group;

$R^5$ is a hydrogen atom or a lower alkyl group;

$R^6$ is a hydrogen or halogen atom, or a lower alkyl, lower alkyloxy or trifluoromethyl group;

Z is O or S; and

*n* is O or the integer 1;

wherein the aryl group as used in the foregoing definitions is a phenyl, substituted phenyl, thienyl or pyridinyl group, the substituted phenyl group having 1 or 2 sub-

stituents independently which are each independently a halogen atom, a lower alkyl, lower alkyloxy or trifluoromethyl group.

2. *N* - {1 - [2 - (4 - Ethyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1 - yl)-ethyl] - 4 - (methoxymethyl) - piperidinyl} - *N* - phenylpropanamide.

3. Methyl 1 - [2 - (4,5 - dihydro - 4 - methyl - 5 - oxo - 1*H* - tetrazol - 1 - yl)-ethyl] - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate.

4. Methyl 1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1 - yl)-ethyl] - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate.

5. Methyl 1 - [2 - (4,5 - dihydro - 5 - oxo - 4 - propyl - 1*H* - tetrazol - 1 - yl)-ethyl] - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate.

6. *N* - {1 - [2 - (4,5 - Dihydro - 4 - methyl - 5 - oxo - 1*H* - tetrazol - 1 - yl)-ethyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide.

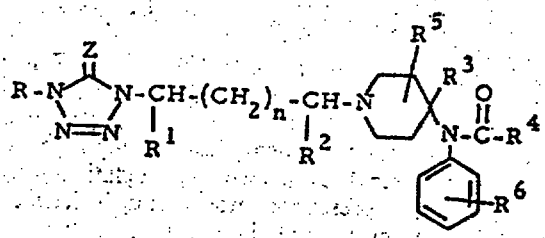
7. N - {1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo - 1*H* - tetrazol - 1 - yl)-1 - methylethyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide.

8. A compound as claimed in claim 1, other than a compound as specifically claimed in any one of claims 2 to 7, substantially as hereinbefore described in the foregoing Examples XI to XXIII.

9. A pharmaceutically acceptable acid addition salt of a compound as claimed in any one of claims 2 to 7.

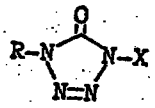
10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active ingredient an effective analgesic amount of a compound as claimed in any one of claims 2 to 8 or a pharmaceutically acceptable addition salt as claimed in claim 9.

11. A process for preparing an *N* - phenyl - *N* - (4 - piperidinyl)amide derivative having the general formula:—



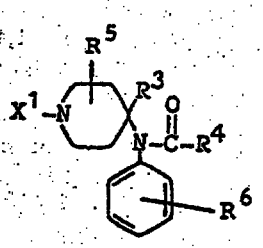
or a pharmaceutically acceptable acid addition salt thereof, wherein R, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, Z and *n* are as defined in claim 1, which process comprises

a) reacting a compound having the formula



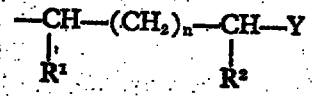
(II)

with a *N*-phenyl-*N*-(4-piperidinyl)amide of the formula



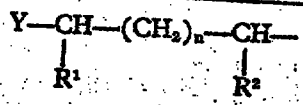
(III)

wherein R, $R^3$, $R^4$, $R^5$ and $R^6$ are as above-defined and either $X^1$ is hydrogen and X is a radical of the formula



(IV)

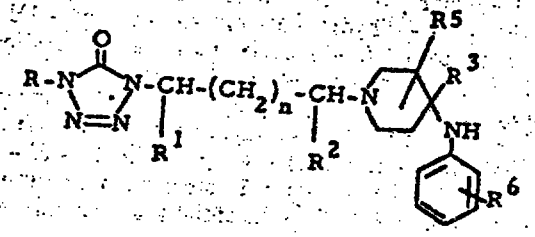
or X is hydrogen and $X^1$ is a radical of the formula



(V)

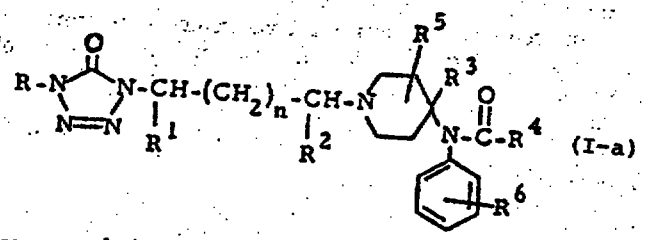
and wherein Y is chloro, bromo, iodo, methylsulfonyloxy, or 4-methylphenylsulfonyloxy residue in a reaction inert organic solvent in the present of a base; or

b) *N*-acylating a compound having the formula



(VI)

according to standard N-acylation procedures in order to prepare a compound having the formula



(I-a)

or c) preparing compounds having the formula (I) wherein Z is S (I-b) by reacting the corresponding compound of formula I in which Z is O with an appropriate sulfurating agent while stirring and heating the reactants together in an appropriate reaction-inert organic solvent or d) debenzylating compounds of the formula (I) wherein R represents phenylmethyl by known debenzylation techniques, in order to prepare compounds, wherein R represents hydrogen and, if desired, preparing pharmaceutically acceptable acid addition salts of the products of steps a) to d), and/or also, if desired resolving racemic mixtures into their stereo-chemically pure isomeric forms by known resolution techniques.

12. A process as claimed in claim 11 wherein reaction (a) is carried out at elevated temperatures.

13. A process for preparing *N* - {1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo-1*H* - tetrazol - 1 - yl)ethyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide which comprises reacting 1 - (2 - chloroethyl) - 4 - ethyl - 1,4 - dihydro-5*H* - tetrazol - 5 - one, with *N* - [4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide.

14. A process for preparing methyl 1 - [2 - (4,5 - dihydro - 4 - methyl - 5-oxo - 1*H* - tetrazol - 1 - yl)ethyl] - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino]-4 - piperidinecarboxylate which comprises reacting 1,4 - dihydro - 1 - (2 - iodoethyl)-4 - methyl - 5*H* - tetrazol - 5 - one with methyl 4 - [*N* - (1 - oxopropyl) - *N*-phenylamino] - 4 - piperidinecarboxylate.

15. A process for preparing methyl 1 -[2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo-1*H* - tetrazol - 1 - yl)ethyl] - 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4-piperidinecarboxylate, which comprises reacting 1 - (2 - chloroethyl) - 4 - ethyl - 1,4-dihydro - 5*H* - tetrazol - 5 - one with methyl 4 - [*N* - (1 - oxopropyl) - *N* - phenylamino] - 4 - piperidinecarboxylate hydrochloride.

16. A process for preparing methyl 1 - [2 - (4,5 - dihydro - 5 - oxo - 4 - propyl-1*H* - tetrazol - 1 - yl)ethyl] - 4 - [*N* - 1 - oxopropyl) - *N* - phenylamino] - 4-piperidinecarboxylate which comprises reacting 1 - (2 - chloroethyl) - 4 - propyl-1,4 - dihydro - 5*H* - tetrazol - 5 - one with methyl 4 - [*N* - (1 - oxopropyl) - *N*-phenylamino] - 4 - piperidinecarboxylate hydrochloride.

17. A process for preparing *N* - {1 - [2 - (4,5 - dihydro - 4 - methyl - 5 - oxo-1*H* - tetrazol - 1 - yl)ethyl] - 4 - (methoxymethyl) - 4 - piperidinyl} - *N* - phenylpropanamide which comprises reacting 1,4 - dihydro - 1 - (2 - iodoethyl) - 4 - methyl-5*H* - tetrazol - 5 - one with *N* - [4 - (methoxymethyl) - 4 - piperidinyl] - *N* - phenylpropanamide.

18. A process for preparing *N* - {1 - [2 - (4 - ethyl - 4,5 - dihydro - 5 - oxo-1*H* - tetrazol - 1 -yl) - 1 - methylethyl] - 4 - (methoxymethyl) - 4 - piperidinyl}-*N* - phenylpropanamide which comprises reacting 1 - ethyl - 1,4 - dihydro - 5*H*-tetrazol - 5 - one with *N* - [1 - (2 - chloropropyl) - 4 - (methoxymethyl) - 4-piperidinyl] - *N* - phenylpropanamide.

19. A process as claimed in claim 11 substantially as hereinbefore described with reference to any one of the foregoing Examples XI to XXIII.

20. A compound as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 11 to 19.

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