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HETEROCYCLO-LOWER ALKANOAMIDOXIME COMPOUNDS

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11 Claims. (Cl. 260—239)

This invention relates to a new series of organic compounds. More particularly, this invention concerns certain heterocyclo-lower alkanoamidoximes, salts thereof and methods for their preparation.

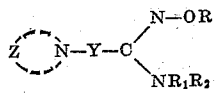
The study of hypertension has occupied a preeminent position both in the research laboratory and in the clinic. The widespread incidence of this disease and the obvious need for effective therapy have prompted an extensive search to find agents which can be used safely in the treatment of hypertensive states both on an acute and on a chronic basis.

In recent years a large number of compounds have come to the foreground as useful hypotensive agents. Among these are various organic synthetics such as guanidines, diguanidines, isothioureas, phthalazines, isoquinolines, halogenated isoindolines, etc., as well as products obtained from natural sources such as the veratrum and Rauwolfia alkaloids. Although these agents possess, to a greater or a lesser degree, hypotensive activity, they are also characterized by having one or more disadvantages as for example, difficulty of preparation, toxicity, short duration of action, or undesirable side effects.

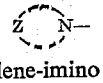
I have now found a new series of compounds which, in addition to the fact that they are effective hypotensive agents, are simple to prepare, relatively non-toxic and chemically unrelated to known hypotensives. In addition to their obvious use as blood-pressure reducing agents in the treatment of various hypertensive states, the compounds of this invention also possess utilitarian value as experimental tools in the pharmacological research laboratory. For example, the new compounds are capable of inhibiting hypertension which has been artificially induced in the experimental animal by amphetamine or ephedrine. Because of this antagonistic action aginst experimental hypertension, the compounds of this invention lend themselves particularly to the study of animal organs during various stages of both mild and severe hypertension.

The doses in which the compounds of this invention may be administered vary considerably depending upon the severity of the hypertensive state, the route employed for administration (oral or parenteral), and the particular compound used. Generally however, it may be stated that the new compounds are effective in dose ranges from 5 mg./kg. body weight to 100 mg./kg. body weight.

The compounds of this invention may be represented by the following general formula:



wherein



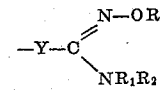
stands for an N,N-alkylene-imino ring, the alkylene radical of which contains from six to nine carbon atoms as chain members, Y represents an alkylene radical containing from one to five carbon atoms, R stands for hydrogen or acyl and R_1 and R_2 each for hydrogen or at least one for lower hydrocarbon, or they form together with the nitrogen a saturated heterocyclic radical.

The alkylene radical Y in the above formula which contains from one to five carbon atoms, is primarily an unbranched carbon chain, e.g. methylene, 1,2-ethylene, 1,4-butylene or 1,5-pentylene, but primarily the 1,3-propylene radical. It may also be branched and represented, for example, by 1,2-propylene.

The radical R in the above formula is preferably hydrogen or may be an acyl radical, especially the acyl radical of a lower alkanoic acid, e.g. acetic, propionic, butyric or pivalic acid, or an aromatic carboxylic acid, e.g. benzoic, di- or tri-methoxy-benzoic or piperonylic acid.

The radicals R_1 and R_2 are preferably both hydrogen, or at least one of them may be a lower hydrocarbon radical containing from one to seven carbon atoms, such as a lower alkyl radical, e.g. methyl, ethyl or propyl. In addition, R_1 and R_2 when taken together with the nitrogen atom, may form a saturated heterocyclic radical such as an N,N-alkylene-imino radical, e.g. pyrrolidino, piperidino, 3- or 4-methyl-piperidino or hexahydroazepino; an N,N-oxaalkylene-imino radical, e.g. morpholino; an N,N-thiaalkylene-imino radical, e.g. thiamorpholino; or an N,N-azaalkylene-imino radical, e.g. N-methyl-piperazino, N-acetyl-piperazino, N-hydroxyethyl-piperazino or N-acetoxyethyl-piperazino.

Thus, the radical of the formula:



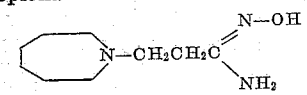
in the above formula stands for a lower alkanoamidoxime, the amidoxime grouping of which may be unsubstituted or substituted as outlined above, and is particularly represented by the acetamidoxime, butyramidoxime, valeramidoxime, caproamidoxime or especially by the propionamidoxime radical.

The heterocyclic radical of the formula:

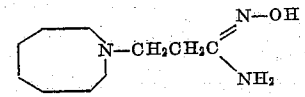


in which Z stands for an alkylene chain containing from six to nine, for example, from six to seven carbon atoms as chain members, is preferably unsubstituted, or, if substituted, contains lower hydrocarbon radicals, such as lower alkyl radicals, e.g. methyl, ethyl or propyl; aromatic radicals, e.g. unsubstituted or substituted phenyl radicals which radicals may also be fused to the alkylene chain Z; or aralkyl radicals, e.g. benzyl or substituted benzyl. Thus, the heterocyclic ring is represented primarily by an unsubstituted hexahydro-1-azepine, octahydro-1-azocine or octahydro-1-azonine radical or by its methyl- or phenyl-substituted homologs.

Outstanding compounds which show particularly strong and long-lasting hypotensive activities are the hexahydro-1-azepine propionamidoxime of the formula:



and its next higher homolog the octahydro-1-azocine propionamidoxime of the formula:

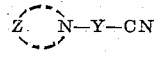


and the acid addition salts thereof, such as the mono- or dihydro-halides, e.g. the dihydrochlorides, thereof.

Also included within the scope of this invention are

the mono- and di-salts of the above-described series of compounds, particularly the therapeutically useful acid addition salts, as for example, those with inorganic acids, such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; perchloric, nitric or thiocyanic acid; sulfuric or phosphoric acids; or those with organic acids, such as, formic, acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, ascorbic, hydroxymaleic, dihydroxymaleic, benzoic, phenylacetic, p-aminobenzoic, p-hydroxybenzoic, anthranilic, cinnamic, mandelic, salicylic, p-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, methane sulfonic, ethane sulfonic, hydroxyethane sulfonic, ethylene sulfonic, benzene sulfonic, p-toluene sulfonic, naphthalene sulfonic or sulfanilic acid or methionine, tryptophane, lysine or arginine. Whether the mono- or the di-salt is obtained depends on the choice of acid and the reaction conditions, e.g. the concentration of the reaction medium.

Although a variety of methods may occur to those skilled in the art for the preparation of amidoximes such as the ones of this invention, a particularly useful method, and one which is intended to be included within the scope of this invention comprises the reaction of a nitrile of the formula:

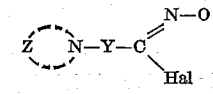


in which Z and Y have the above given meaning, with hydroxylamine, particularly in the form of an acid addition salt thereof such as the hydrohalide, e.g. hydrochloride or hydrobromide; or the sulfate. The reaction is preferably carried out in an alkaline medium, especially in such cases in which a hydroxylamine salt is used, to ensure liberation of the hydroxylamine base. A suitable alkaline medium is a solution of an alkali metal lower alkanolate which is preferably used in a lower alkanol solution, for example, potassium methylate in methanol or sodium ethylate in ethanol. Alternatively, if so desired, one may employ an alkali metal hydroxide or carbonate, as for example sodium or potassium hydroxide, or sodium carbonate or potassium hydrogen carbonate.

The nitriles used as starting materials in the above reaction may be prepared by reacting the desired heterocycle for example, hexahydroazepine, octahydroazocine or octahydroazonine with a halogenated aliphatic nitrile. The reaction is advantageously conducted in a suitable non-polar organic solvent medium such as for example xylene, toluene or, preferably, benzene. There are no particular limitations as to time or temperature since the reaction proceeds even at room temperature. Obviously however, in order to get a maximum yield of product as quickly as possible, it is desirable to conduct the reaction under reflux conditions. When so conducted over a period of about ½ to about 3 hours, a maximum yield of the nitrile intermediate can be obtained.

Where, in the above-described general formula, the aliphatic chain Y represents an ethylene radical, the intermediate heterocyclo-propionitrile may be conveniently prepared by reacting the heterocycle, for example, hexahydroazepine or octahydroazocine, with acrylonitrile. The reaction proceeds spontaneously and exothermically although the maximum yield of product can be obtained in the shortest period of time by conducting the reaction under reflux conditions. No additional solvent is necessary in this case since the acrylonitrile itself serves this purpose.

Amidoximes, in which the free amino group is replaced by a substituted amino group as characterized in the above-depicted formula by the radical —NR_1R_2, in which at least one of the radicals R_1 and R_2 represents a lower hydrocarbon radical or when taken together with the nitrogen atom form a saturated heterocyclic radical, may be prepared according to a different method. Instead of using the nitriles as starting materials the corresponding aldehydes are converted into the aldoximes by treatment of an ethanolic solution of the aldehyde with hydroxylamine, especially in the form of a salt thereof, e.g. the hydrochloride. The free hydroxyl group may be, if desired, acylated, e.g. benzoylated. Upon halogenation, such as chlorination with chlorine, preferably used in a chloroform or hydrochloride solution, or with nitrosylchloride, particularly in cold ether, the corresponding hydroximic acid halide of the formula:



in which



R, and Y have the above given meaning and Hal stands for a halogen, especially a chlorine atom, is formed, which, especially in ether solution, reacts with a primary or secondary amine to yield the desired N-substituted amidoxime. Primary amines are especially lower alkyl amines, e.g. methyl- or ethylamine; secondary amines are di-lower alkyl amines, e.g. dimethylamine or diethylamine; or N,N-alkylene-imines such as pyrrolidine, piperidine or hexahydroazepine, morpholine or a piperazine derivative.

Amidoximes in which the hydroxyl groups is acylated by the acyl radical of a lower alkanoic or an aromatic carboxylic acid are prepared by usual acylating methods. Thus, the acyl radical may be introduced by reacting the amidoxime with the halide, e.g. chloride, or the anhydride of a carboxylic acid, preferably in an inert solvent, e.g. ether, hexane, benzene or toluene, and, if desired, in the presence of an alkaline reagent, e.g. sodium or potassium hydroxide, carbonate or hydrogen carbonate. The acylated amidoxime may be obtained in the form of its hydrohalic acid addition salt, e.g. the hydrochloride, if the acylation reaction is performed in the absence of a base, or in the form of the free base, especially if an anhydride is used as the acylating agent.

According to the working conditions the desired amidoxime may be obtained in the form of the free base or as an acid addition salt thereof. A free base may be obtained from its salts by treatment with a base, e.g. sodium or potassium hydroxide, carbonate or hydrogen carbonate. Salts may be prepared from the free base by reacting a solution, e.g. an ethanolic solution, or etheral solution, of the base with an acid, such as one of those mentioned above.

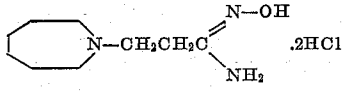
This application is a continuation-in-part application of my application Serial No. 658,006, filed May 9, 1957, now abandoned.

The following examples illustrate the process of the present invention but are not to be construed as being limitative thereon. Temperatures are given in degrees centigrade.

Example 1

30.4 g. of hexahydro-1-azepinepropionitrile is added to a solution of about 13.9 g. of hydroxylamine hydrochloride in 300 ml. of anhydrous ethanol. A solution of sodium ethylate containing 4.6 g. of sodium in 150 ml. of anhydrous ethanol is slowly added to the mixture with stirring. After the addition is completed, the reaction mixture is refluxed for 3 hours and allowed to stand at room temperature for 72 hours. Solid material is filtered from the reaction mixture and the filtrate concentrated under reduced pressure to give a pale yellow oil of hexahydro-1-azepine-propionamidoxime. The dihydrochloride of this product is formed by dissolving the oil in anhydrous ethanol, gassing with dry hydrogen chloride and

adding ether. The precipitate hexahydro-1-azepine propionamidoxime dihydrochloride of the formula:

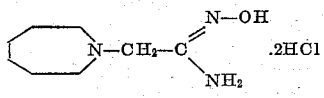


is recrystallized from ethanol, M.P. 183–185° (with decomposition).

The starting material used in the above reaction may be prepared as follows: 50 g. of hexahydroazepine is slowly added to 212 g. of acrylonitrile with stirring. During the addition the reaction mixture warms up; trimethylbenzylammonium hydroxide in 38% aqueous solution (Triton B) is added after the initial reaction subsides and the mixture is refluxed for about 1½ hours. Stirring is continued overnight at room temperature, the excess acrylonitrile is removed under reduced pressure and the residual liquid is fractionated to give hexahydro-1-azepine propionitrile, B.P. 121–123° C./14 mm.; $n_D^{30}=1.4710$.

Example 2

13.8 g. of hexahydro-1-azepine acetonitrile is added to a solution of 6.95 g. of hydroxylamine hydrochloride in 300 ml. of absolute ethanol. An ethanolic solution of sodium ethylate, made up of 2.3 g. of sodium in 100 ml. of absolute ethanol is slowly added to the above solution. Stirring is continued at room temperature for 24 hours, the solution is then filtered and the filtrate concentrated under reduced pressure to a yellow oil of hexahydro-1-azepine-acetamidoxime. By adding ethanolic hydrogen chloride to this product there is formed the hexahydro-1-azepine acetamidoxime dihydrochloride of the formula:

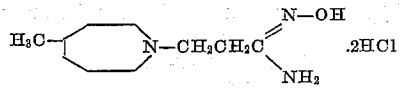


which on recrystallization from a mixture of ethanol and ether melts at 171–173° C.

The starting material used in the above reaction may be prepared as follows: To 25 g. of chloroacetonitrile in 350 ml. of benzene there is slowly added, with cooling and stirring, 33 g. of hexahydroazepine. The solution is refluxed for one hour, cooled and made alkaline with 1N sodium hydroxide solution. The benzene layer is separated, dried, and after concentration under reduced pressure, the residual oil is factionated to give hexahydro-1-azepine acetonitrile, a colorless oil, B.P. 102–103° C./14 mm.

Example 3

About 16.6 g. of hexahydro-4-methyl-1-azepine propionitrile is added with stirring to a solution of 6.95 g. hydroxylamine hydrochloride in 400 ml. of ethanol. To this solution is slowly added an ethanolic solution of sodium ethylate (2.3 g. of sodium in 115 ml. of ethanol). After stirring for 96 hours, the solution is filtered and the ethanol removed under reduced pressure. Addition of ethanolic hydrogen chloride and ether to the residual oil gives the desired dihydrochloride of hexahydro-4-methyl-1-azepine propionamidoxime of the formula:

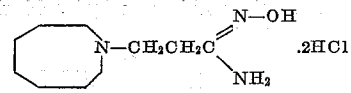


M.P. 165–175° C.

The starting material used in the above reaction may be prepared as follows: 20 g. of hexahydro-4-methyl-azepine is slowly added with stirring to 38 g. of acrylonitrile. The solution becomes slightly warm and after the addition of 3 ml. of Triton B (trimethyl benzyl ammonium hydroxide) it becomes very warm and stirring is continued overnight. The excess acrylonitrile is removed under reduced pressure and the residual oil fractionated to give hexahydro-4-methyl-1-azepine propionitrile, B.P. 126–130° C./15 mm.

Example 4

16.6 g. of the octahydro-1-azocine propionitrile is added with stirring to a solution of 6.95 g. of hydroxylamine hydrochloride in 250 ml. of absolute ethanol. To this mixture, a solution of 2.3 g. of sodium in 100 ml. of absolute ethanol is added slowly. Stirring is continued overnight at room temperature. The solution is filtered, and the filtrate concentrated under reduced pressure. Treatment of the residual oil with ethanolic hydrogen chloride and then with ether gives the octahydro-1-azocine propionamidoxime dihydrochloride of the formula:



M.P. 180–185° C.

The starting material used in the above reaction may be prepared as follows: 14.3 g. of octahydroazocine is slowly added to 27.6 g. of acrylonitrile with stirring. The addition of 2 ml. of Triton B causes a vigorous reaction to occur and the solution is stirred at room temperature overnight. After the excess acrylonitrile is removed under reduced pressure, the residual oil is fractionated under reduced pressure to give octahydro-1-azocine propionitrile, B.P. 94–97°/0.9 mm.

Example 5

An ethanolic solution of equal molecular amounts of hexahydro-1-azepine propionic acid thioamide and hydroxylamine hydrochloride is treated with sufficient aqueous sodium carbonate solution to liberate the hydroxylamine base from the salt. The solution is then heated under reflux for 18 hours and the reaction is complete when evolution of hydrogen sulfide ceases. After ether extraction of the aqueous solution, the ether solution is gassed with dry hydrogen chloride to form the dihydrochloride of hexahydro-1-azepine propionamidoxime identical with the product obtained according to the procedure described in Example 1.

The starting material used in the above-described reaction may be prepared as follows: 15 g. of hexahydro-1-azepine propionitrile dissolved in 25 ml. of ethanol is treated with 80 ml. of an ethanolic solution of ammonia and then saturated with hydrogen sulfide. The stoppered flask is kept at room temperature for 2 days after which the hexahydro-1-azepine propionic acid thioamide is removed by filtration.

Example 6

23.45 g. of ethyl hexahydro-1-azepine propionimidate is treated with a concentrated solution of 6.95 g. of hydroxylamine hydrochloride in 10 ml. of water with stirring. After standing for several days and ether extraction, the residual solution gives the desired dihydrochloride of hexahydro-1-azepine propionamidoxime after treatment with alkali, chloroform extraction and conversion of the base contained in the chloroform extract to the dihydrochloride, which is identical with the compound obtained according to the process described in Example 1.

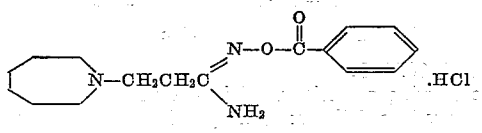
The starting material used in the above reaction may be prepared as follows: 3.65 g. of hydrogen chloride gas is bubbled into 15.2 g. of hexahydro-1-azepine propionitrile dissolved in a mixture of 6 ml. of absolute ethanol and 50 ml. of ether; during the reaction the mixture is cooled in an ice bath. During the addition of hydrogen chloride an additional 10 ml. of absolute ethanol is added to the mixture, followed by 50 ml. of ether. The solution is kept in the refrigerator several days during which time crystallization occurs. The ethyl hexahydro-1-azepine propionimidate dihydrochloride is removed by filtration and dried under reduced pressure over concentrated sulfuric acid and solid sodium hydroxide.

Example 7

The monohydrochloride of hexahydro-1-propionamidoxime, M.P. 164–166°, is prepared by treating a concentrated ethanolic solution of the base with hydrogen chloride gas.

Example 8

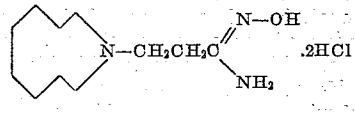
To a solution of 3 g. of hexahydro-1-azepine propionamidoxime (Example 1) in 200 ml. of ether is slowly added while cooling and stirring a solution of 2.29 g. of benzoyl chloride in 10 ml. of ether. After standing overnight, the solution is filtered and the O-benzoyl hexahydro-1-azepine propionamidoxime hydrochloride of the formula:



is recrystallized from a mixture of ethanol and ether, M.P. 153–155°.

Example 9

A solution of 6.56 g. of hydroxylamine hydrochloride in 150 ml. of absolute ethanol is treated with 17 g. of octahydro-1-azonine propionitrile while stirring. To this mixture is slowly added a solution of sodium ethylate in ethanol (2.15 g. of sodium in 75 ml. of ethanol) and the reaction mixture is refluxed for 3 hours, then stirred at room temperature overnight. After filtration the ethanol is removed from the filtrate under reduced pressure and addition of ethanolic hydrogen chloride to an ethanol solution of the residual oil yields the dihydrochloride of octahydro-1-azonine propionamidoxime of the formula:

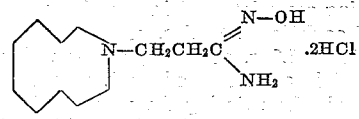


M.P. 173–176° (with decomposition).

The starting material used in the reaction may be prepared as follows: 20.5 g. of octahydroazonine is slowly added to 35 g. of acrylonitrile while stirring. The addition of 2 ml. of Triton B causes a vigorous exothermic reaction. The solution is refluxed for one and one half hours and the excess acrylonitrile then removed under reduced pressure. The residual oil is fractionated, the octahydro-1-azonine propionitrile boiling at 83–85°/1 mm., n_D^{30}=1.4815.

Example 10

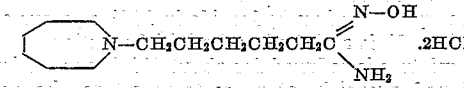
To a solution of 6.95 g. of hydroxylamine hydrochloride in 150 ml. of absolute ethanol is added 19.4 g. of decahydro-1-azecine propionitrile and the mixture is treated carefully with a solution of sodium ethylate in ethanol (2.3 g. of sodium in 75 ml. of ethanol) and then refluxed for three hours. After stirring overnight at room temperature and filtering, the ethanol is removed under reduced pressure and the ethanolic solution of the oily residue is treated with ethanolic hydrogen chloride to yield the dihydrochloride of decahydro-1-azecine propionamidoxime of the formula:



The starting material used in the reaction may be prepared as follows: 14.1 g. of decahydroazecine is slowly added to 21.2 g. of acrylonitrile while stirring. The addition of 2 ml. of Triton B causes an exothermic reaction which is maintained by refluxing for several hours. The excess of acrylonitrile is removed under reduced pressure and the decahydro-1-azecine propionitrile is purified by fractioned distillation under reduced pressure.

Example 11

To a mixture of 19.4 g. of hexahydro-1-azepine-capronitrile and 6.95 g. of hydroxylamine hydrochloride in 400 ml. of absolute ethanol is slowly added an ethanolic solution of sodium ethylate (2.3 g. of sodium in 115 ml. of ethanol). After standing at room temperature for 96 hours the mixture is filtered and the ethanol removed under reduced pressure. Upon addition of ethanolic hydrogen chloride to the ethanolic solution of the oily residue the dihydrochloride of hexahydro-1-azepine caproamidoxime of the formula:



is collected.

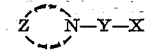
The starting material used in the reaction may be prepared as follows: A solution of 50 g. of hexahyroazepine in a mixture of 50 ml. of benzene and 10 ml. of chloroform is treated with 33.2 g. of ε-chlorocapronitrile while stirring and refluxing over a period of 5 hours. After standing overnight at room temperature, the solution is filtered, the filtrate concentrated under reduced pressure and the hexahydro-1-azepine capronitrile collected by fractionated distillation, M.P. 97–110°/0.5 mm.

Example 12

7.0 g. of hexahydro-2-oxo-1-azepine propionamidoxime is placed into the extractor of a Soxhlet apparatus and extracted into a slurry of 2.01 g. of lithium aluminum hydride in 1500 ml. of ether. The process is maintained for 72 hours by refluxing the hydrogenation mixture while stirring. The extractor is then removed, the remaining starting material is added directly to the reaction flask together with an additional 500 ml. of ether and the mixture is boiled for an additional 6 hours. After cooling 10 ml. of water-saturated ether, then 20 ml. of water are added dropwise, the mixture is acidified with 5 N aqueous sulfuric acid and extracted three times with 200 ml. of ether. The aqueous layer is separated, made basic with a 40% aqueous solution of sodium hydroxide and extracted three times with chloroform, which solution is dried over sodium sulfate. On concentrating under reduced pressure a light yellow oil is obtained which solidifies on cooling and yields a dihydrochloride identical with the one obtained according to Example 1.

The starting material used in the above reaction may be prepared as follows: To a mixture of 4.35 g. of hydroxylamine hydrochloride in 200 ml. of absolute ethanol is added dropwise 12 g. of hexahydro-2-oxo-1-azepine propionitrile, obtained by reacting hexahydro-2-oxo-azepine with acrylonitrile. The mixture is treated with an ethanolic solution of sodium ethoxide (1.5 g. of sodium in 60 ml. of absolute ethanol) and refluxed while stirring during 3 hours. After stirring for an additional 16 hours at room temperature the mixture is filtered and concentrated under reduced pressure to yield the hexahydro-2-oxo-1-azepine propionamidoxime, M.P. 160–165°.

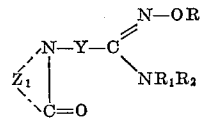
Generally the amidoximes of this invention may be obtained by reacting a compound of the formula:



in which Z and Y have the above given meaning and X stands for a nitrogen-containing derivative of a carboxyl or a thiocarboxyl group, with hydroxylamine or a salt thereof; such derivatives are, for example, the nitriles, thioamides and iminoethers, e.g. the iminoethylether. The conditions for such conversions have been described in detail hereinbefore for the treatment of nitriles with hydroxylamine. The starting materials are known or, if unknown, may be prepared according to procedures known for the preparation of compounds containing such groups. Thus, thioamides may be prepared by treatment

of a nitrile with an ethanolic solution of ammonia and hydrogen sulfide. Iminoethers and salts thereof, such as the iminoethylether, may be prepared by treatment of a nitrile with an alcoholic, e.g. ethanolic, solution of a hydrogen halide, e.g. hydrogen chloride.

A further method for the preparation of the amidoximes of the present invention consists in treating amidoximes of the formula:



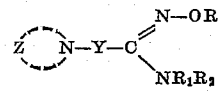
in which Y, R, R_1 and R_2 have the above given meaning and Z_1 represents an alkylene radical containing from 5 to 8 carbon atoms as chain members, with an agent capable of reducing a carbonyl group of an amide to a methylene group. Such agents are especially di-light metal hydrides, particularly lithium aluminum hydride. The starting material used in this reaction may be prepared according to known methods; for example, caprolactam may be heated with acrylonitrile, the nitrile thus formed converted to the amidoxime by reaction with hydroxylamine hydrochloride. The reduction with lithium aluminum hydride then furnishes the desired hexahydro-1-azepine propionamidoxime.

The invention also comprises any modification of the process wherein a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining step(s) of the process are carried out, as well as any new intermediates.

In the process of this invention such starting materials are preferably used which lead to final products mentioned hereinbefore as preferred embodiments of the invention.

What is claimed is:

1. A member of the group consisting of compounds of the formula:



in which the radical



stands for an alkyleneimino ring, the alkylene radical of which contains from six to nine carbon atoms as chain members, Y represents an alkylene radical containing from one to five carbon atoms, R stands for a member of the group consisting of hydrogen, the acyl radical of an unsubstituted lower alkanoic acid, the acyl radical of benzoic acid, the acyl radical of methoxy-substituted benzoic acid and the acyl radical of piperonylic acid, and each of the radicals R_1 and R_2 stands for a member of the group consisting of hydrogen, lower hydrocarbon, and when taken together with the nitrogen, of an N,N-alkyleneimino radical, the alkylene radical of which contains from 4 to 6 carbon atoms, and therapeutically useful acid addition salts thereof.

2. Hexahydro-1-azepine propionamidoxime.

3. Hexahydro-1-azepine propionamidoxine dihydrochloride.

4. Octohydro-1-azocine propionamidoxime.

5. Hexahydro-1-azepine acetamidoxime.

6. Hexahydro-4-methyl-1-azepine propionamidoxime.

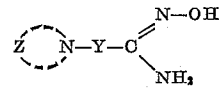
7. O-benzoyl hexahydro-1-azepine propionamidoxime.

8. Octahydro-1-azonine propionamidoxime.

9. Hexahydro-1-azepine caproamidoxime.

10. Process for the preparation of hexahydro-1-azepine propionamidoxime which comprises treating hexahydro-1-azepine propionitrile with hydroxylamine hydrochloride in the presence of sodium ethylate in ethanol.

11. A compound of the formula



in which the radical



stands for an alkyleneimino ring, the alkylene radical of which contains from six to seven carbon atoms, and Y represents an alkylene radical containing from one to five carbon atoms.

No references cited.

UNITED STATES PATENT OFFICE

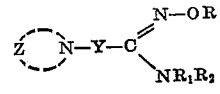
Certificate of Correction

Patent No. 2,897,195 July 28, 1959

Robert Paul Mull

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 1, lines 61 to 65, the formula should appear as shown below instead of as in the patent:



Signed and sealed this 15th day of December 1959.

[SEAL]

Attest:
KARL H. AXLINE,
Attesting Officer.

ROBERT C. WATSON,
Commissioner of Patents.