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CERTAIN AMINOALKYL HYDRAZIDINES

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ABSTRACT OF THE DISCLOSURE

Compounds of the formula

$$R(CH_2)_nC(=NH)NHNH_2 \cdot HCl$$

wherein R is di(lower)alkylamino, pentamethyleneimino, hexamethyleneimino, heptamethyleneimino or dimethoxyphenyl and *n* is an integer from 1–2 are decongestant or hypertensive agents.

This invention relates to chemical compounds of the formula:

$$R(CH_2)_nC(=NH)NHNH_2 \cdot nHCl$$

wherein R is a member of the group consisting of di(lower)alkylamino, pentamethyleneimino, hexamethyleneimino, heptamethyleneimino and 3,4-dimethoxyphenyl; and *n* is an integer from 1–2.

The compounds of this invention when administered intravenously to dogs in a dose of 0.1 mg./kg. produce vasoconstriction. At larger doses of about 10–25 mg./kg. an elevation of blood pressure is elicited. Thus they are useful as decongestant or hypertensive agents.

Methods for preparing the compounds of this invention consist of: A. Reacting a nitrile of the formula

$$R(CH_2)_nCN$$

wherein R and *n* have the significance above given with sodium hydrazide followed by treatment with hydrochloric acid to produce the salt. The reaction is carried out at low temperature and in an inert atmosphere to insure optimal results. In conducting the reaction the following apparatus has been found to be advantageous:

A 1000 ml. 3 neck flask equipped with a reflux condenser, special stirrer of the type described in Chem. Ber., 95:1540 (1962), dropping funnel, nitrogen inlet and a thermometer was used as the reaction apparatus. A Teflon blade stirrer was used which was effective in removing caking from the bottom of the flask and breaking up rising gas bubbles. Above the agitator blade a bell filled with paraffin oil was attached to the stirring rod with a rubber stopper. The bell prevented the loss of lubricant (paraffin oil) in the lower part of the agitator assembly, caused by condensing or splattering solvent and the washing of sodium hydrazide against the stirrer bearing. One source of danger, the ignition of the sodium hydrazide by the agitator, could thus be eliminated. In order to avoid excessive pressure in the system, a mercury "bubbler valve" was placed between the nitrogen pressure tank and the apparatus. The reflux condenser was equipped with a trap containing mineral oil. This trap was the closure of the apparatus and served simultaneously as a bubble counter for the escaping gas. All ground glass joints were secured with coil springs or wire. During the conversion a protective shield was placed in front of the apparatus.

Using such apparatus the following synthese exemplify the preparation of members of the series of compounds of this invention.

EXAMPLE I

2-diethylaminoacetimidic acid hydrazide dihydrochloride

Into the described apparatus was placed 20 g. (0.5 mole) of sodium amide with 200 ml. of anhydrous ether. An ethereal solution of 16 g. (0.5 mole) of anhydrous hydrazine was added dropwise to a cold (0.5°) suspension of sodium amide. After the hydrazine had been added, the gray suspension was allowed to warm to 10° over a 2 to 3 hour period. The suspension was then cooled to 0–5° before 63 g. (0.5 mole) of 2-diethylaminoacetonitrile was added dropwise. The creamy-white suspension was allowed to warm to 20° over a 1½ hour period. The suspension was cooled to 0–5° and treated with 18 ml. (1.0 mole) of water and stired for an additional ½ hour to assure decomposition of the sodium salt and then filtered via vacuum. The residue and flask were washed with three 100 ml. portions of dry ether. The ethereal solution was dried for 1 hour over sodium sulfate and then concentrated under vacuum. The oily residue was distilled under vacuum and the first fraction containing the starting nitrile came over at 40–60°/0.3 mm. (about 10 g.). The second fraction distilled at 60–78°/0.3 mm. (about 3 g.) and the 2-diethylaminoacetimidic acid hydrazide came over at 78–80°/0.3 mm. The yield amounted to 32–40 g. (46–65%) of product which is converted to the hydrochloride salt as follows:

Conversion to the hydrochloride salt: After cooling, 400 ml. of acetonitrile was saturated with hydrogen chloride and added in small portions to a warm (about 60°) solution of 2-diethylaminoacetimidic acid hydrazide in 800 ml. of acetonitrile. After each portion of HCl-acetonitrile was added, the flask was shaken until all of the solid dissolved. This procedure was continued until it became apparent that no more solid was redissolving and the dihydrochloride had been formed. The acetonitrile suspension was heated for an additional 10 minutes or until boiling. The salt suspension was cooled to room temperature and then immersed in an ice bath to facilitate complete precipitation of the dihydrochloride having a melting point of 170–174°. This was recrystallized from ethanol to a constant melting point of 175–177° (corrected).

Analysis.—Calc. for $C_6H_{18}N_4Cl_2$: C, 33.19; H, 8.36; N, 25.80. Found: C, 33.16; H, 8.40; N, 25.84.

EXAMPLE II

2-azepinoacetimidic acid hydrazide dihydrochloride

Into the apparatus described was placed 14.4 g. (0.3 mole NaH) of 50% sodium hydride in mineral oil with 300 ml. of dry ether. An ethereal solution of 9.6 g. (0.3 mole) of anhydrous hydrazine was added dropwise to a cold (0.5°) suspension of sodium hydride. After the hydrazine had been added, the gray to white suspension was allowed to awrm to 10–15° C. over a 2 hour period. The suspension was then cooled to 0–5° C. before the addition of 41.4 g. (0.3 mole) of azepenoacetonitrile. The creamy-white suspension was allowed to warm to 15° C. for 1½ hours. The suspension was cooled to 0–5° C. and treated with 14 ml. of water and stirred for an additional 1 hour and then filtered via vacuum. The ether solution was decanted from any aqueous layer and dried over anhydrous sodium sulfate for 1 hour. The ethereal solution was concentrated and the residue was distilled. The product distilled at: 135° (0.8 mm. Hg); 114–126° (0.3 mm. Hg) or 126° (0.5 mm. Hg) to yield 17.4 g. (29%). The free base was converted to the dihydrochloride according to the directions in Example I having an M.P. of 190–192° C. This was recrystallized from ethanol to a constant melting point of 195–196° C. (corrected).

Analysis.—Calc. for $C_8H_{20}Cl_2N_4$: C, 39.51; H, 8.29; N, 23.04. Found: C, 39.51; H, 8.48; N, 23.01.

EXAMPLE III

2-piperidinoacetimidic acid hydrazide dihydrochloride

Into the apparatus described was placed 21.6 (0.45 mole) of 50% sodium hydride in mineral oil with 300 ml. of dry ether. An ethereal solution of 16 g. (0.5 mole) of anhydrous hydrazine was added dropwise to a cold (0–5° C.) suspension of sodium hydride. After the hydrazine had been added, the gray-white suspension was allowed to warm to 10° over a two hour period. The suspension was then cooled to 0–5° C. before an ethereal solution of 49.6 g. (0.4 mole) of piperidinoacetonitrile was added dropwise. The creamy-white suspension was allowed to warm to 15° C. for 1½ hours. The suspension was cooled to 0–5° C. and treated with 18 ml. of water and stirred for an additional one hour and then filtered via a vacuum. The ether solution was decanted from any aqueous layer and dried over anhydrous sodium sulfate for one hour. The etheral solution was concentrated and the residue distilled. There was a forerun of 10 g., B.P. 60–85° (0.2 m. Hg). The product distilled at 90–92° (0.2 mm. Hg), to yield 13 g. (20%). The free base was converted to the dihydrochloride according to the directions in Example I having an M.P. of 191–195° C. This was recrystallized from ethanol to a constant melting point of 200–201° C. (corrected).

Analysis.—Calc. for $C_7H_{18}Cl_2N_4$: C, 36.73; H, 7.98; N, 24.52. Found: C, 36.69; H, 7.92; N, 24.45.

B. Reacting a nitrile of the formula $R(CH_2)_nCN$ wherein R and *n* have the significance given above with methanolic hydrogen chloride to form the corresponding imidate and treatment of that imidate with formylhydrazide followed by methanolysis to secure the hydrazidine. In carrying out this course of reactions it is advantageous to observe anhydrous conditions and maintain an inert atmosphere in order to obtain best results.

Exemplary syntheses of members of this series of compounds are the following:

EXAMPLE IV

A. N-formamido-3-dimethylaminopropionamidine hydrochloride

A solution of 100 ml. of 3-dimethylaminopropionitrile in 700 ml. of absolute methanol was treated with dry HCl at 10–20° over ca. 3 hours, until saturated, using mechanical stirring. The resultant solution was diluted with anhydrous ether. The white crystalline product was collected under anhydrous conditions washing with ca. 1 l. of anhydrous ether having an M.P. of 99–100°. The yield was 118 g. To a mixture of 105 g. (0.52 mole) of the imidate dihydrochloride and 960 ml. of absolute alcohol was added dropwise 78 ml. (0.57 mole) of triethylamine, at 2–4°, using rapid stirring. Then 35.0 g. (0.58 mole) of formylhydrazide was added at 4–7° in ca. 1 minute. The temperature was maintained at 5–7° for 15 minutes, allowed to gradually rise to 13° in 25 minutes, and to 23° over 2½ hours by exposure to room temperature. The mixture was cooled to 10° and the white crystalline product was collected, washing with four 20-ml. portions of ethanol and with ether. Dried in a vacuum desiccator (over Drierite) overnight the product weighed 62 g. (61%). Recrystallized from ca. 300 ml. of ethanol, the purified product, M.P. 119–121°; weighed 32 g.

B. 3-(dimethylamino)propionimidic acid hydrazide

The product of A., 90 g. (0.46 mole), was treated with 270 ml. of ice-cold, dry HCl—CH_3OH solution, cooling in an ice bath. The resultant solution was allowed to gradually warm in the atmosphere over 40 minutes; a crystalline, white solid deposited. The mixture was cooled in an ice bath, and the crude product was collected, washing with 10-ml. portions of CH_3OH, ethanol and two 10-ml. portions of isopropanol and ether. Dried in a vacuum desiccator overnight, the solid was recrystallized from 300 ml. of CH_3OH, washing with 10 ml. of CH_3OH, two 10-ml. portions of ethanol, three 10-ml. portions of isopropanol, and ether, to give 44 g. (47%); M.P. 158–159°.

Analysis.—Calc. for $C_5H_{14}N_4 \cdot 2HCl$: C, 29.56; H, 7.94; N, 27.58. Found: C, 29.81; H, 8.00; N, 27.54.

EXAMPLE V

A. N-formamido-2-(3,4-dimethoxyphenyl)acetamidine

A solution of 100 g. (0.57 mole) of homoveratronitrile in 500 ml. of anhydrous methanol was treated with dry HCl at 10–15° over 1⅓ hr., until saturated, using mechanical stirring. The resultant solution was concentrated to ⅓ volume, under the water aspirator, heating on the steam bath. When the concentrated solution was diluted with anhydrous ether to a volume of ca. 1 l., a white crystalline solid deposited. The solid was collected, washing with ca. 800 ml. of anhydrous ether. Dried in a vacuum desiccator over Drierite overnight, the product, M.P. 141–147° (melted at 109–112° and resolidified), weighed 85 g. (61%).

To a mixture of 101 g. (0.41 mole) of methyl 2-(3,4-dimethoxyphenyl)acetimidate hydrochloride and 500 ml. of absolute alcohol was added 57 ml. (0.42 mole) of triethylamine (dried over NaOH) at 2–4° in 13 min., using rapid stirring. Then 26 g. (0.43 mole) of formylhydrazide was added immediately, at 2–3°, and the temperature was maintained at 2–3° for ½ hr. The temperature was allowed to rise to 8° in 20 min., and maintained at 8° for 3½ hr. The resultant white crystalline solid was collected, washing with three 20-ml. portions of ethanol, two 20-ml. portions of isopropanol, and with ether having an M.P. of 114–118° to yield 67 g. (69%). Recrystallized from absolute alcohol, the M.P. is raised to 126–128°.

B. 2-(3,4-dimethoxyphenyl)acetimidic acid hydrazide hydrochloride

The product of A., 19 g. (0.08 mole), was treated with 55 ml. of cold, dry HCl—CH_3OH solution, cooling in an ice bath. The solid immediately dissolved and a white crystalline solid quickly deposited. After standing at room temperature for ½ hr., the mixture was again cooled, and the product was collected, washing with two 5-ml. portions of ethanol, three 5-ml. portions of isopropanol and ether to yield 18 g. This was recrystallized from ca. 300 ml. of ethanol to give an M.P. of 198–200°.

Analysis.—Calc. for $C_{10}H_{15}N_3O_2 \cdot 2HCl$: C, 48.90; H, 6.52; N, 17.12. Found: C, 49.00; H, 6.48; N, 17.18.

EXAMPLE VI

A. N-formamido-3-piperidinopropionamidine dihydrochloride

A solution of 70 ml. of 3-piperidinopropionitrile in 560 ml. of absolute methanol was treated with dry HCl at 10–20° in 70 min. The resultant solution was added to 1 l. of anhydrous ether, triturated and decanted from the solid residue. Repeated trituration with anhydrous ether (1800 ml. total), followed by decantation, afforded a crystalline solid. The solid was collected, washing with ca. 800 ml. anhydrous ether to give 61 g., M.P. 170–172°.

To a mixture of 71 g. (0.29 mole) of the imidate dihydrochloride and 379 ml. of absolute alcohol was added dropwise 35.6 ml. (0.26 mole) of triethylamine at 2–3° in ca. 5 min., using rapid stirring. Then 21 g. (0.35 mole) of formylhydrazide was added at 3–4° in ca. 1 min. The temperature was maintained at 5–7° for ½ hr. and at 9–10° for 1½ hr. The mixture was cooled in an ice bath for 1 hr. and the insoluble triethylamine hydrochloride was collected. The filtrate was treated with 42 ml. of dry HCl-isopropanol solution to a pH of 4–5, cooling in an ice bath. After standing in the cold for ½ hr., the white, crystalline solid was collected, washing with three 30 ml.

portions of isopropanol and with ether to yield 40.5 g., M.P. 156–158°, (51%). The product was recrystallized in two 20 g. portions, using 60 ml. of ethanol for each to yield 26 g., M.P. 157–159°.

B. 3-piperidinopropionimidic acid hydrazide dihydrochloride

The product of A., 52.5 g. (0.19 mole), was treated with 158 ml. of dry HCl—CH_3OH solution, cooling in an ice bath. The mixture was allowed to warm in the atmosphere for ½ hr. The resultant white crystalline solid was collected, washing with three 10-ml. portions of ethanol, three 10-ml. portions of isopropanol and with ether to yield 292 g., M.P. 179–181°.

Analysis.—Calc. for $C_8H_{18}N_4 \cdot 2HCl$: C, 39.63; H, 8.31; N, 23.11. Found: C, 39.70; H, 8.26; N, 22.93.

EXAMPLE VII

A. N-formamido-3-(hexahydro-1H-azepino)-propionamidine dihydrochloride

A solution of 100 ml. of 3-hexahydro-1H-azepinopropionitrile in 494 ml. of absolute methanol was treated with dry HCl at 5–20° in 70 min. The resultant solution was treated with anhydrous ether (1 l.), triturated and decanted from the amorphous residue. Repeated trituration with anhydrous ether (total of ca. 2 l.) followed by decantation, afforded a pinkish-colored, crystalline solid. The solid was collected, washing well with ether to yield 115 g., M.P. 151–162°.

To a mixture of 115 g. (0.45 mole) of the imidate dihydrochloride and 829 ml. of absolute alcohol was added dropwise 62.5 ml. (0.45 mole) of triethylamine at 2–4° in ca. 5 min., using rapid stirring. Then 26.6 g. of formylhydrazide was added to 3–5° in ca. 1 min. The temperature was maintained at 5–6° for ½ hour, and at 9–10° for 2½ hr. The mixture was cooled to 2°, and the insoluble triethylamine hydrochloride was collected. The filtrate was treated with 60 ml. of dry HCl-isopropanol to a pH of 2–3, cooling in an ice bath. A white crystalline solid was collected, washing well with ethanol isopropanol and ether to yield 76 g. (59%), M.P. 154–157°. Recrystallized in three portions, the product melted at 157–159.5°, 153.5–157° and 158.5–161°.

B. 3-(hexahydro-1H-azepino)propionimidic acid hydrazide dihydrochloride

The product of A., 86 g. (0.30 mole), was treated with 258 ml. of dry HCl—CH_3OH solution, cooling in an ice bath. The mixture was allowed to warm in the atmosphere for ¾ hour and again cooled in an ice bath for ½ hour. A white crystalline solid was collected, washing with two 40-ml. portions of ethanol, two 40 ml. portions of isopropanol and ether to yield 66 g., M.P. 175–177°. Recrystallized from 800 ml. of SDA-30, washing with two 20-ml. portions of ethanol, three 20-ml. portions of isopropanol and ether, the product melted at 178–179.5°.

Analysis.—Calc. for $C_9H_{20}N_4 \cdot 2HCl$: C, 42.02; H, 8.62; N, 21.78. Found: C, 42.25; H, 8.50; N, 21.75.

EXAMPLE VIII

A. 3-(1-heptamethyleneimino)-N-formamido-propionamidine dihydrochloride

Heptamethyleneimine, 20 g. (0.12 mole), was added dropwise to 180 ml. (0.26 mole) of acrylonitrile at 25–26° in 10 min., using mechanical stirring. The reaction solution was heated to 57° and an additional 20 g. of heptamethyleneimine was added at 54–57°. Then 0.9 ml. of benzyltrimethyl-ammonium hydroxide was added at 40–49°, and the mixture was refluxed on the steam bath for 2½ hours. After stirring overnight at room temperature the mixture was stripped of solvent. The residue was extracted with ca. 200 ml. of ether, the extract was stripped of solvent, and the crude product was distilled, using a Claisen head. Collected at 112–117°/ 30–32 min., the product, 3-(1-heptamethyleneimino)propionitrite, weighed 45.7 g. (88%).

A solution of 20 ml. of 3-(heptamethyleneimino)propionitrile in 110 ml. of absolute methanol was treated with dry HCl at 5–12° until saturated. The reaction mixture was allowed to warm to 20° and added to ca. 500 ml. of anhydrous ether. An oily material deposited. After trituration, the supernatant liquid was decanted and the process was repeated with fresh ether for 3 or 4 times, until the residue was crystalline. The resultant solid was collected, washing well with ether, and dried in a vacuum desiccator (over Drierite) overnight to yield 23 g. of methyl 3-(heptamethyleneimino) propionimidat dihydrochloride.

A mixture of 43 g. (0.16 mole) of methyl 3-(heptamethyleneimino) propionimidate dihydrochloride and 300 ml. of absolute alcohol was treated dropwise at 1–4° with 23 ml. (0.17 mole) of triethylamine, in 3 min., using mechanical stirring. Then 9.7 g. (0.16 mole) of formic acid hydrazide was added at 3–4°. The temperature was maintained at 5–6° for 25 min. and at 9–10° for 1 hour. A white, crystalline solid (triethylamine hydrochloride) was collected. The filtrate was treated with ca. 35 ml. of dry HCl-isopropanol solution to a pH of 2, cooling in an ice bath. The resultant white crystalline solid was collected, washing with four 10-ml. portions of isopropanol, and ether. Dried in air for ½ hour and in a vacuum desiccator over Drierite overnight, the initial product, slightly damp with alcohol, weighed 54 g. When dried, the product, 25 g., was recrystallized from 70 ml. of ethanol to yield 9.3 g. (42%), M.P. 163–165°.

B. 3-(1-heptamethyleneimino)propionimidic acid hydrazide dihydrochloride

The product of A., 29 g. (0.097 mole), was treated with 90 ml. of a solution of dry HCl in methanol, cooling in an ice bath. The mixture was allowed to stand at room temperature for ½ hour, with intermittent handstirring, and then cooled in an ice bath for ½ hour. A white, crystalline solid was collected, washing with ethanol and ether to yield 9.5 g. (36%), M.P. 166–168°.

Analysis.—Calc. for $C_{10}H_{22}N_4 \cdot 2HCl$: C, 44.30; H, 8.92; N, 20.65. Found: C, 44.32; H, 8.84; N, 20.92.

What is claimed is:

1. A compound of the formula:

$$R(CH_2)_n\overset{\overset{NH}{\|}}{C}NHNH_{2-n}HCl$$

wherein

R is a member of the group consisting of di(lower) alkylamino, pentamethyleneimino, hexamethyleneimino, heptamethyleneimino, and 3,4-dimethoxyphenyl;

and

n is an integer from 1–2.

2. A compound according to claim 1 wherein the compound is 2-diethylaminoacetimidic acid hydrazide dihydrochloride.

3. A compound according to claim 1 wherein the compound is 2-azepinoacetimidic acid hydrazide dihydrochloride.

4. A compound according to claim 1 wherein the compound is 2-piperidinoacetimidic acid hydrazide dihydrochloride.

5. A compound according to claim 1 wherein the compound is 3-dimethylaminopropionimidic acid hydrazide dihydrochloride.

6. A compound according to claim 1 wherein the compound is 2(3,4-dimethoxyphenyl)acetamidic acid hydrazide dihydrochloride.

7. A compound according to claim 1 wherein the compound is 3-piperidinopropionimidic acid hydrazide dihydrochloride.

8. A compound according to claim 1 wherein the compound is 3-(hexahydro-1H-azepino)propionimidic acid dihydrochloride.

9. A compound according to claim 1 wherein the compound is 3-(1-heptamethyleneimino)propionimidic acid hydrazide dihydrochloride.

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