United States Patent

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[31] **10341/66**

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[54] **1,4 ENDOMETHYLENE CYCLOHEXANE-2,3 ENDO-CIO DI CARBOXIMIDO GLUTARIMIDES**

3 Claims, No Drawings

[52] **U.S. Cl.** ..... **260/281,** 260/326.5 FM, 260/343.2, 260/343.6, 260/346.3, 260/514 R, 260/557 R, 260/557 B, 424/267

[51] **Int. Cl.** **C07d 31/32**

[50] **Field of Search** ..... 260/281, 282, 343.2, 326.5 FM, 287

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ABSTRACT: Cyclic derivatives of succinic and glutaric acids are described, which are substituted by imide groups derived from specific cyclic dicarboxylic acids. The derivatives according to the invention are free of an aromatic phthalimide grouping and exhibit a tranquilizing activity on certain parts of the central nervous system, whereas they are free of embryotoxic (teratogenous) secondary effects when administered to pregnant mammals.

1,4 ENDOMETHYLENE CYCLOHEXANE-2,3 ENDO-CIO DI CARBOXIMIDO GLUTARIMIDES

This invention relates to a new class of derivatives of succinic and glutaric acids, more particularly, to anhydrides and, imides of succinic and glutaric acids, which are substituted by imide groups derived from specific cyclic dicarboxylic acids. The invention also relates to a process of producing these novel compounds.

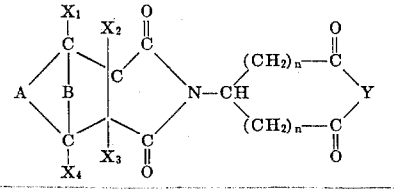
Some known substituted succinimides and glutarimides which contain phthalimide groups in the alpha or beta position have a tranquilizing activity on certain portions of the central nervous system and differ from other conventional sedatives and hypnotics, such as barbituric acids, hydantoins, etc., in that the action is not accompanied by an initial excitation phase and there is a complete absence of narcotic or peripheral paralytic effects. Besides, the novel compounds have an extremely low acute toxicity and basically differ also in this respect from other previously used drugs having the same indication. The therapeutical activity is obtained quickly after oral or parenteral administration and is maintained for a relatively long time.

The agents of the above-mentioned type, particularly the compounds known as thalidomides, have a serious disadvantage residing in the embryotoxic (teratogenous) secondary effects, which occur after the administration to pregnant women and often result in serious malformations of the infant. In spite of their undeniable advantages as outlined above, the use of these agents has been entirely prohibited in numerous countries for the reasons given.

The present invention is based on the discovery that this undesired embryotoxic activity is due to a specific part of the structure, namely, the aromatic phthalimide structure.

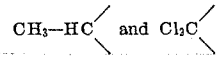
Surprisingly it has been found that the use of other dicarboxylic acids having cyclic, bicyclic and related ring systems rather than phthalic acid results in previously unknown compounds, which are of therapeutic significance and have qualitatively the same pharmacological activities as the previously known succinimides and glutarimides of the class defined hereinbefore, whereas the danger of an occurrence of teratogenous effects is entirely eliminated with these new compounds.

The compounds according to the present invention have the general formula



wherein A and B each represent a bivalent hydrocarbon radical, which may be saturated or unsaturated, in the simplest case a methylene, ethylene or vinylidene grouping, or a larger radical, which may have a linear, branched-chain, cyclic, bicyclic, aromatic or polynuclear configuration, B may also represent an oxygen atom or two hydrogen atoms, each of which is bound to the carbon atom bearing substituents X_1 and X_4; the hydrocarbon radicals represented by A and/or B may be substituted by halogen, alkyl, aryl, cycloalkyl, aralkyl, alkylidene or arylidene groups, X_1–X_4 each represent hydrogen, halogen or alkyl group substituents, which may be substituted, particularly by oxygen or oxygen-containing radicals, X_2 and X_3 together may represent a double bond, Y represents an oxygen atom, or a nitrogen atom in which the third valence is partly saturated by hydrogen or a hydrocarbon radical, and the subscripts *n* represent integers between 0 and 2.

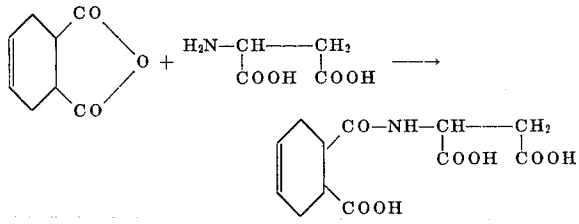
A preferably represents groups such as —CH_2—CH_2—, —CH=CH— and O—phenylene, B preferably represents two hydrogen atoms, a methylene or ethylene radical or an oxygen atom. Further examples of B are phenylene, isopropylidene, diphenylethylene or substituted methylene radicals, such as



Examples of substituents on the imide nitrogen are lower alkyl groups, e.g., methyl, ethyl, any of the various propyl, butyl or allyl groups etc.; cyclohexyl; aryl, aralkyl and alkaryl groups, e.g., phenyl, benzyl, p-toluyl, etc.

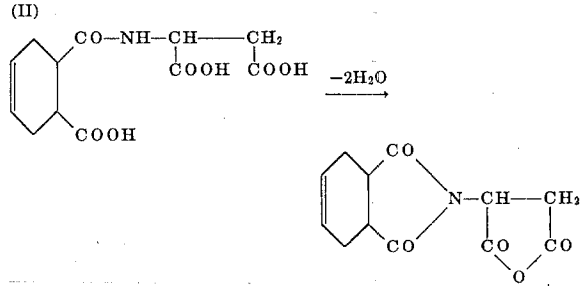
These novel compounds can be produced by methods in which the corresponding cyclic or polycyclic dicarboxylic acids, which can easily be obtained as products of Diels-Alder reactions, or specific reactive functional derivatives thereof, particularly their anhydrides, chlorides or esters, are reacted with aminodicarboxylic acids, e.g., with alpha-aminosuccinic acid (aspartic acid) or alpha-aminoglutaric acid (glutamic acid) or suitable derivatives thereof, such as their esters, amides, diamides or imides. To facilitate an understanding, this reaction step and the following ones will be explained with reference to tetrahydrophthalic anhydride as an example of the (poly) cyclic dicarboxylic acid and to aspartic acid as an example of the aminodicarboxylic acid component. The following reaction results:

(I)



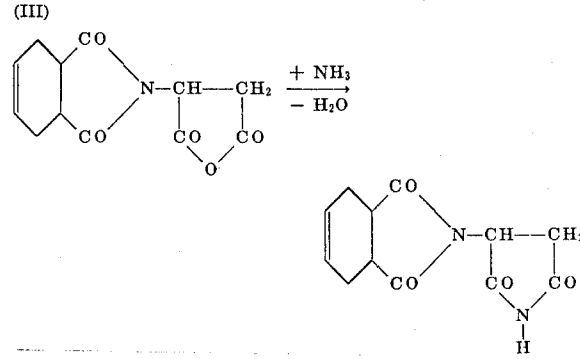
The intermediate products obtained in reaction are transformed by treatment with a dehydrating agent, such as acetic anhydride, acetyl chloride, $POCl_3$ or the like, into the corresponding dicarboximidosuccinic or dicarboximidoglutaric anhydrides, e.g.,

(II)



Finally, the anhydrides are reacted with ammonia, its salts, such as NH_4Cl or $(NH_4)_2CO_3$ or other NH_3-yielding compounds, such as urea, thiourea, guanidine, guanidine salts, formamide, acetamide or the like, to form the cyclic imides:

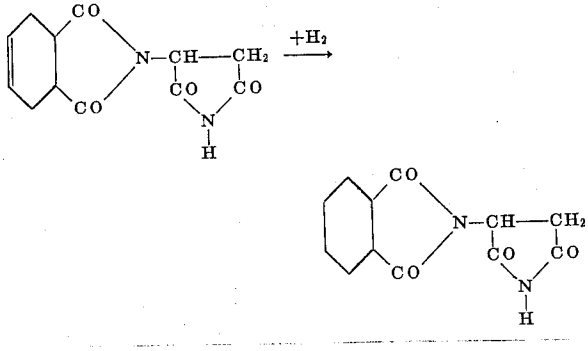
(III)



Instead of ammonia, primary amines or compounds which can liberate primary amines in situ may be used in the immediately preceding reaction step so that the corresponding N-substituted succinic imides of succinic or glutaric acid are obtained.

If the resulting products contain double bonds capable of hydrogenation, they may be transformed in the usual manner into the saturated compounds. If two or more double bonds capable of hydrogenation and of different reactivity are present, one or more of them may be selectively saturated (partial hydrogenation).

(IV)



The process which has been outlined above may be modified in various ways. A listing of all modifications which are possible is impossible and impractical for reasons of space. The examples which will be given hereinafter are intended only to illustrate the multiplicity of the existing possibilities. The fact that no specific synthetic route is mentioned has no restricting significance.

As has been mentioned above, the cyclic imides of aminodicarboxylic acids rather than the free aminodicarboxylic acids may be used in the first reaction step so that the starting products are subjected to the transformation of the anhydride into an imide otherwise carried out in step III.

Monoamides of aminodicarboxylic acids, e.g., asparagine, glutamine, isoasparagine or isoglutamine, may be used instead of the free aminodicarboxylic acids to obtain the end products of step III in the second reaction step.

The same applies to the use of the diamides. In this case the cyclization (according to step III) takes place with the elimination of NH_3.

The introduction of the other imide group into the compounds according to the invention may be similarly modified. For instance, a cyclic or polycyclic dicarboxylic imide may be reacted with a suitable reactive derivative of succinic acid or glutaric acid, e.g., the reaction of the potassium salt of 1,4-endomethylene-Δ^5-cyclohexene-2,3-dicarboxylic imide with diethyl alpha-bromosuccinate results in the formation of diethyl 1,4-endomethylene-Δ^5-cyclohexene-2,3-dicarboximidosuccinate. This ester is transformed into the imide (according to III) by reaction with NH_3 followed by treatment with acetylchloride.

In another modification of the process, the Diels-Alder reaction to form the cyclic or polycyclic dicarboxylic component is carried out at the end of the sequence of reactions. For instance, alpha-maleinimidoglutarimide reacts with conjugated dienes to form the corresponding cyclic or polycyclic dicarboximidoglutarimides.

The compounds prepared according to the invention may be used as therapeutics alone or in combination with other agents and adjuvants or as intermediates in the preparation of therapeutics. They may also be used as starting products of further syntheses.

EXAMPLE 1

Twenty grams of DL-aspartic acid and 23 grams of Δ^4-cyclohexene-1,2-cis-dicarboxylic anhydride were boiled in 80 ml. of absolute pyridine to complete dissolution. The solvent was then removed in vacuo and the residue, together with 50 ml. of acetic anhydride was shortly heated to boiling. Δ^4-cyclohexene-1,2-cis-dicarboximidosuccinic anhydride crystallized upon cooling. Melting point 192°–193° C. Yield 31.5 grams.

$C_{12}H_{11}NO_5$ (249.22): Calculated 5.62 percent N, found 5.60 percent N.

Twenty-five grams of the above anhydride were finely ground together with 10 grams of urea and the resulting mixed powders were heated on an oil bath to 180° C. for 30 minutes. The cooled mass was received in dimethylformamide (DMF). Δ^4-cyclohexene-1,2-cis-dicarboximidosuccinimide precipitated upon addition of water. Melting point 190°–192° C., yield 19.5 grams.

$C_{12}H_{12}N_2O_4$ (248.24): Calculated 11.29 percent N, found 11.17 percent N.

The same product was obtained in analogous experiments in which ammonium chloride, ammonium carbonate, thiourea, guanidine sulfate or acetamide was used rather than urea.

Hydrogenation: The above imide was dissolved in ethanol and hydrogenated in the presence of a charcoal-supported palladium catalyst. The catalyst was filtered off and the solvent was removed in vacuo. The resulting cyclohexane-1,2-cis-dicarboximidosuccinimide has a melting point of 156°–158° C.

$C_{12}H_{14}N_2O_4$ (250.25): Calculated 11.20 percent N, found 11.15 percent N.

EXAMPLE 2

Twenty grams of DL-aspartic acid and 25 of grams 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboxylic anhydride were reacted in the procedure of example 1 to form the 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidosuccinic anhydride, melting point 170°–171° C., yield 36.5 grams.

$C_{13}H_{11}NO_5$ (261.23): Calculated 5.36 percent N, found 5.56 percent N.

Thirty grams of the above anhydride together with 20 grams of ammonium carbonate were heated to 180°–200° C. for 30 minutes. The mass was cooled and received in water. The solution was extracted in an extractor with ether to exhaustion. The ether solution was evaporated and the residue was dissolved in aqueous acetone, from which 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidosuccinimide was crystallized. Melting point 212°–213° C., yield 21 grams.

$C_{13}H_{12}N_2O_4$ (260.25): Calculated 10.77 percent N, found 10.90 percent N.

Hydrogenation of the above imide using the procedure of example 1 resulted in 1,4-endomethylene-cyclohexane-2,3-endo-cis-dicarboximidosuccinimide, melting point 260°–262° C., $C_{13}H_{14}N_2O_4$ (262.26): Calculated 10.68 percent N, found 10.86 percent N.

EXAMPLE 3

Thirty-eight grams of L-glutamic acid and 40 of grams Δ^4-cyclo-hexene-1,2-cis-dicarboxylic anhydride were boiled in 120 ml. of pyridine to complete dissolution. The pyridine was then distilled off and the residue was heated together with 120 ml. of acetic anhydride. The volatile matter was then removed in vacuo. Grinding the residue in ether resulted in the formation of crystalline Δ^4-cyclohexene-1,2-cis-dicarboximidoglutaric anhydride, melting point 166°–167° C.

$C_{13}H_{14}NO_5$ (263.24): Calculated 5.32 percent N, found 5.27 percent N.

Twelve grams of the above anhydride were reacted using the procedure of example 1 with 6 grams urea to form Δ^4-

cyclohexene-1,2-cis-dicarboximidoglutarimide. Melting point 194°–195° C.

$C_{13}H_{14}N_2O_4$ (262.26): Calculated 10.68 percent N, found 10.59 percent N.

The hydrogenation of the above imide using the procedure of example 1 resulted in cyclohexane-1,2-cis-dicarboximidoglutarimide. Melting point 180°–181° C.

$C_{13}H_{16}N_2O_4$ (264.28): Calculated 10.60 percent N, found 10.66 percent N.

EXAMPLE 4

Twenty-nine grams of L-glutamic acid and 30 grams of cyclohexane-1,2-cis-dicarboxylic anhydride were reacted using the procedure of example 1 to form cyclohexane-1,2-cis-dicarboximidoglutaric anhydride, melting point 171°–172° C.

$C_{13}H_{15}NO_5$ (285.27): Calculated 5.28 percent N, found 5.26 percent N.

The above anhydride was transformed by the procedure of example 1 to form cyclohexane-1,2-cis-dicarboximidoglutarimide, melting point 180°–181° C. This product proved to be identical to that described in example 3.

$C_{13}H_{16}N_2O_4$ (262.28): Calculated 10.60 percent N, found 10.51 percent N.

EXAMPLE 5

Twenty-nine grams of L-glutamic acid and 30 grams of cyclohexane-1,2-trans-dicarboxylic anhydride were reacted using the procedure of example 1 to form cyclohexane-1,2-cis-dicarboximidoglutaric anhydride, melting point 170°–172°. By its mixed melting point and its infrared spectrum, this product was proved to be identical to the compound described in example 4.

EXAMPLE 6

Forty-five grams of L-glutamic acid and 53 grams of 1,4-endo-methylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboxylic anhydride were boiled together with 150 ml. pyridine for 2 hours. After cooling, the mixture was filtered and evaporated in vacuo. The residue was boiled up with 100 ml. of acetic anhydride and reevaporated to one-half its volume. Part of the resulting 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutaric anhydride crystallized upon cooling and was filtered off. An addition of ether to the mother liquor resulted in a quantitative precipitation. Melting point 175°–176° C.

$C_{14}H_{13}NO_5$ (275.28): Calculated 5.09 percent N, found 5.14 percent N.

Twenty-seven grams of the above anhydride were reacted together with 12 grams of urea using the procedure of example 1. The first precipitate consisted of 18 grams of 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutarimide. Further amounts of this product were recovered by extraction of the aqueous solution with ether to exhaustion using the procedure of example 2.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22 percent N, found 10.29 percent N.

The hydrogenation of the above imide using the procedure of example 1 resulted in 1,4-endomethylene-cyclohexane-2,3-endo-cis-dicarboximidoglutarimide, melting point 235°–236° C.

$C_{14}H_{16}N_2O_4$ (276.29): Calculated 10.14 percent N, found 10.21 percent N.

EXAMPLE 7

32.5 grams of L-glutamic acid and 36 grams of 1,4-endomethylene-Δ^5-cyclohexene-2,3-exo-cis-dicarboxylic anhydride, were reacted by the procedure of example 6 to form 1,4-endomethylene-Δ^5-cyclohexene-2,3-cis-dicarboximidoglutaric anhydride, melting point 214°–216° C.

$C_{14}H_{13}NO_5$ (275.25): Calculated 5.09 percent N, found 5.06 percent N.

Using the procedure of example 1, the above anhydride was transformed into 1,4-endomethylene-Δ^5-cyclohexene-2,3-exo-cis-dicarboximidoglutarimide, melting point 241°–243° C.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22 percent N, found 10.19 percent N.

The hydrogenation of the above imide in the procedure of example 1 resulted in 1,4-endomethylene-cyclohexane-2,3-exo-cis-dicarboximidoglutarimide, melting point 259°–260° C.

$C_{14}H_{16}N_2O_4$ (276.29): Calculated 10.14 percent N, found 10.05 percent N.

EXAMPLE 8

Forty-five grams of L-glutamic acid and 53 grams of 1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboxylic anhydride were reacted using the procedure of example 6 to form 1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboximidoglutaric anhydride, melting point 214°–216° C.

$C_{14}H_{15}NO_5$ (277.28): Calculated 5.05 percent N, found 5.12 percent N. Five grams of the above anhydride were charged into 30 ml. of concentrated ammonia. The solution was allowed to stand for several hours and then evaporated. The residue was boiled for 1 hour together with 30 ml. of acetic anhydride, then completely dried in vacuo. The glassy residue was dissolved in aqueous dimethylformamide, from which 1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboximidoglutarimide was crystallized. Melting point 235° C. The mixed melting point and the infrared spectrum proved this product to be identical to that obtained in example 6.

$C_{14}H_{16}N_2O_4$ (276.29): Calculated 10.14 percent N, found 10.29 percent N.

EXAMPLE 9

41.5 grams of L-glutamic acid and 50 grams of 1,4-endoethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboxylic anhydride were reacted using the procedure of example 6 to form 1,4-endoethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutaric anhydride, melting point 246°–248° C.

$C_{15}H_{15}NO_5$ (289.28): Calculated 4.84 percent N, found 4.84 percent N. Using the procedure of example 1, the above anhydride was transformed into 1,4-endoethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutarimide, melting point 240°–242° C.

$C_{15}H_{16}N_2O_4$ (288.29): Calculated 9.72 percent N, found 9.74 percent N.

The hydrogenation of the above imide by the procedure of example 1 resulted in 1,4-endoethylenecyclohexane-2,3-cis-dicarboximidoglutarimide, melting point 248°–250° C.

$C_{15}H_{18}N_2O_4$ (290.31): Calculated 9.65 percent N, found 9.72 percent N.

EXAMPLE 10

29.5 grams of L-glutamic acid and 35.6 grams of methyl-1,4-endomethylene-Δ^5-cyclohexane-2,3-cis-dicarboxylic anhydride (Diels-Alder adduct of maleic anhydride and methyl cyclopentadiene) were reacted by the procedure of example 1. The product corresponding to methyl-1,4-endomethylene-Δ^5-cyclohexene-2,3-cis-dicarboximidoglutaric anhydride was crystallized only with difficulty and was subjected to further processing without purification. Part of the product was crystallized out of a mixture of glacial acetic acid and acetic anhydride for analysis. Melting point 171°–173° C.

$C_{15}H_{15}NO_5$ (289.28): Calculated 4.84 percent N, found 4.98 percent N.

The above product was transformed into methyl-1,4-endomethylene-Δ^5-cyclohexene-2,3-cis-dicarboximidoglutarimide by heating with ammonium carbonate according to the procedure of example 2. Melting point 204°–208° C.

$C_{15}H_{16}N_2O_4$ (288.30): Calculated 9.72 percent N, found 9.78 percent N.

EXAMPLE 11

18.3 grams of L-glutamic acid and 21 grams of 1,4-endoxocyclohexane-2,3-exo-cis-dicarboxylic anhydride were boiled in 100 ml. of pyridine to complete dissolution. The pyridine was then largely removed in vacuo. The residue was received in dilute H_2SO_4 and the solution was extracted with either to exhaustion. The residue obtained by the distillation of the ether was boiled up together with 40 ml. of acetic anhydride. 1,4-endoxcyclohexane-2,3-exo-cis-dicarboximidoglutaric anhydride crystallized upon cooling. Melting point 219°–220° C., yield 19.7 grams.

$C_{13}H_{13}NO_6$ (279.24): Calculated 5.02 percent N, found 4.96 percent N.

Sixteen grams of the above anhydride were reacted with 10 grams of urea using the procedure of example 1 to form 1,4-endoxocyclohexane-2,3-exo-cis-dicarboximidoglutarimide, melting point 329°–330° C., yield 13 grams.

$C_{13}H_{14}N_2O_5$ (278.26): Calculated 10.07 percent N, found 10.19 percent N.

EXAMPLE 12

16.3 grams of L-glutamic acid and 41.2 grams of 1,4,5,6,7,7-hexachloro-1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboxylic anhydride (Diels-Alder adduct of maleic anhydride and hexachlorocyclopentadiene) were reacted by the procedure of example 1 to form 1,4,5,5,6,7,7-hexachloro-1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutaric anhydride, melting point 235°–240° C., yield about 25 grams.

C_{14} $H_7Cl_6NO_5$ (481.97): Calculated 2.91 percent N, found 3.01 percent N.

Eighteen grams of the above anhydride were reacted with 10 grams of urea by the procedure of example 1 to form 1,4,5,6,7,7-hexachloro-1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutarimide, melting point 266°–268° C., yield 14 grams.

$C_{14}H_8Cl_6N_2O_4$ (480.98): Calculated 5.82 percent N, 44.24 percent Cl, found 5.67 percent N, 43.75 percent Cl.

EXAMPLE 13

29.5 grams of L-glutamic acid and 55.5 grams of 5,6; 7,8-dibenzo-bicyclo(2,2,2,)octane-2,3-cis-dicarboxylic anhydride (Diels-Alder adduct of maleic anhydride and anthracene) were reacted using procedure of example 1 to form 5,6; 7,8-dibenzo-bicyclo(2,2,2)octane-2,3-cis-dicarboximidoglutaric anhydride. Melting point 283°–285° C. Yield 58 grams.

$C_{23}H_{17}NO_5$ (387.39): Calculated 3.62 percent N, found 3.69 percent N.

The above anhydride was transformed into 5,6; 7,8-dibenzobicyclo(2,2,2)octane-2,3-cis-dicarboximidoglutarimide by heating with urea or ammonium carbonate. Melting point 283°–284° C.

$C_{23}H_{18}H_2O_4$ (386.41): Calculated 7.25 percent N, found 7.27 percent N.

EXAMPLE 14

6.7 grams of L-glutamic acid and 15 grams of 7-diphenylmethylene-1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboxylic anhydride (partially hydrogenated Diels-Alder adduct of maleic anhydride and diphenylfulvene) were reacted using the procedure of example 1 to form 7-diphenylmethylene-1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboximidoglutaric anhydride, melting point 254°–256° C.

$C_{27}H_{23}NO_5$ (441.49): Calculated 3.17 percent N, found 3.22 percent N.

The above anhydride was transformed by the procedure of example 1 into 7-diphenylmethylene-1,4-endomethylenecyclohexane-2,4-endo-cis-dicarboximidoglutarimide, melting point 210°–212° C.

$C_{27}H_{24}N_2O_4$ (440.51): Calculated 6.36 percent N, found 6.23 percent N.

EXAMPLE 15

Twenty grams of a freshly prepared potassium compound of 1,4-endomethylene-Δ^5cyclohexene-2,3-endo-cis-dicarboxylic acid imide and 25 grams of diethyl alpha-bromosuccinate were heated together with 100 ml. of dimethylformamide on a water bath for 1 hour. After cooling, the solvent was removed in vacuo. The residue was received in water and repeatedly shaken with ether. The combined ether extracts were dried over Na_2SO_4, filtered and evaporated. The resulting diethyl alpha-(1,4-endo-methylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-succinate was received in absolute ethanol without further purification. The solution was saturated with dry ammonia gas with stirring and cooling and was then left undisturbed for a prolonged time. It was thereafter evaporated to dryness in vacuo. The residue was treated to 50 ml. of acetyl chloride, reevaporated and finally received in glacial acetic acid. Storage in a refrigerator caused part of the resulting 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido-succinimide to crystallize. Further parts precipitated upon dilution with water. Melting point 212°–213 °C.

$C_{13}H_{12}N_2O_4$ (260.25): Calculated 10.77 percent N, found 10.82 percent N.

EXAMPLE 16

Ten grams of L-alpha-aminosuccinic acid-gamma-amide (L-asparagine) and 12.5 grams of 1,4-endomethylene-Δ^5-2,3-endo-cis-dicarboxylic anhydride were boiled in 50 ml. of pyridine to complete dissolution. The pyridine was then largely removed in vacuo. Four hundred and thirty milliliters of acetyl chloride were added to the residue. The resulting mixture was heated on a water bath for 1 hour and was then evaporated. When the cooled mass was ground with acetone, 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidosuccinimide was crystallized. Melting point 212° C., yield 11.5 grams.

$C_{13}H_{12}N_2O_4$ (260.25): Calculated 10.77 percent N, found 10.68 percent N.

EXAMPLE 17

Ten grams of L-alpha-aminoglutaric acid-delta-amide (L-glutamine) and 11.5 grams of 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboxylic anhydride were reacted using the procedure of example 16 to form 1,4-endomethylene-Δ^5-cyclohexene- 2,3-endo-cis-dicarboximidoglutarimide, melting point 235°–236° C.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22 percent N, found 10.09 percent N.

EXAMPLE 18

Ten grams of DL-alpha-aminoglutarimide and 15 grams of 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboxylic anhydride were boiled in 50 ml. of pyridine. The solution was filtered and evaporated in vacuo. The residue was shortly boiled with a little glacial acetic acid and acetic anhydride. 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutarimide crystallized together with other products upon storage in a refrigerator and was obtained in a pure state by repeated recrystallization from aqueous dimethylformamide. Melting point 235° C.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22 percent N, found 9.98 percent N.

EXAMPLE 19

27.5 grams of 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutaric anhydride obtained by the procedure of example 6 were finely ground with 77.5 grams of methylamine hydrochloride and heated to 180°–190° C. on an oil bath for 1 hour. The cooled mass was received in acetone. The surplus methylamine hydrochloride separated and was removed. The product was freed from acetone and recrystallized from aqueous dimethyl formamide: N-methyl-alpha-

(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide, melting point 153°–154° C., yield about 24 grams.

$C_{15}H_{16}N_2O_4$ (288.30): Calculated 9.72 percent N, found 9.88 percent N.

EXAMPLE 20

5.5 grams of N-methyl-alpha-(maleinimido)-glutarimide were dissolved in 40 milliliters of dimethylformamide and 5 grams of freshly distilled cyclopentadiene were added to the solution. When the latter had been stored for 24 hours, it was evaporated in vacuo to one-third of its original volume. After the addition of water and storage in a refrigerator, N-methyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide was crystallized. Melting point 152°–154° C.

$C_{15}H_{16}N_2O_4$ (288.30): Calculated 9.72 percent N, found 9.84 percent N.

EXAMPLE 21

27.5 grams of 1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutaric anhydride obtained by the procedure of example 6 were melted together with 10 grams of benzylamine. The cooled mass was dissolved in aqueous dimethylformamide whereby N-benzyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide was crystallized. Melting point 137°–138° C.

$C_{21}H_{20}N_2O_4$ (364.39): Calculated 7.71 percent N, found 7.75 percent N.

The above imide was hydrogenated to produce N-benzyl-alpha-(1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboximido)-glutarimide, melting point 168°–170° C.

$C_{21}H_{22}N_2O_4$ (366.41): Calculated 7.65 percent N, found 8.03 percent N.

Analogous procedures resulted in the formation of: N-phenyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide, melting point 220° C.; N-phenyl-alpha-(1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboximido)-glutarimide, melting point 212° C.; N-(p-toluyl)-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide, melting point 243° C.; N-(p-toluyl)-alpha-(1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboximido)-glutarimide, melting point 232° C.; N-cyclohexyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide, glassy mass.

EXAMPLE 22

1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutaric anhydride produced by the procedure of example 6 was charged in small increments with stirring into an aqueous solution of an excess of methylamine and was allowed to stand overnight at room temperature. The solution was then evaporated in vacuo to dryness. The glassy residue was boiled up together with an equal amount of acetic anhydride and reevaporated in vacuo. The residue was dissolved in ethanol. N-methyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide was crystallized from the solution. Melting point 153°–154° C. This product was identical to that obtained in example 19.

Hydrogenation: The above product was hydrogenated in the presence of a charcoal-supported palladium catalyst. This was followed by filtering and evaporation in vacuo. The residue was dissolved in ethanol, from which N-methyl-alpha-(1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboximido)-glutarimide was crystallized. Melting point 138°–139° C.

$C_{15}H_{18}N_2O_4$ (290.32): Calculated 62.05 percent C, 6.25 percent H, 9.65 percent N; found 62.04 percent C, 6.21 percent H, 9.70 percent N.

Analogous procedures resulted in the formation of: N-ethyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide, melting point 147°–148° C.; N-n-propyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide oily; N-n-butyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide, melting point 186° C.; N-allyl-alpha-(1,2-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide, oily; N-t-butyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide, melting point 198° C.

EXAMPLE 23

Twenty grams of 1,4-endomethylene-Δ^5-cyclohexene-2,3--exo-cis-dicarboximidoglutaric anhydride produced by the procedure of example 7 were heated together with 10 grams of methylamine hydrochloride at 180°–190° C. for 1 hour. The cooled mass was dissolved in a little dimethylformamide, diluted with water and extracted with ether. The ether extract was evaporated. The residue was dissolved in ethanol, from which N-methyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-exo-cis-dicarboximido)-glutarimide was crystallized. Melting point 170°–172° C.

$C_{15}H_{16}N_2O_4$ (288.30): Calculated 9.72 percent N, found 9.84 percent N.

The hydrogenation of the above product resulted in N-methyl-alpha-(1,4-endomethylenecyclohexane-2,3-exo-cis-dicarboximido)-glutarimide, melting point 181° C.

$C_{15}H_{18}N_2O_4$ (290.32): Calculated 62.05 percent C, 6.25 percent H, 9.65 percent N; found 61.89 percent C, 6.20 percent H, 9.70 percent N.

EXAMPLE 24

14.5 grams of 1,4-endothylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutaric anhydride obtained by the procedure of example 9 were reacted with methylamine hydrochloride using the procedure of example 23. N-methyl-alpha-(1,4-endoethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-glutarimide, melting point 185°–186° C.

$C_{16}H_{18}N_2O_4$ (303.54): Calculated 9.27 percent N, found 9.18 percent N.

The above product was hydrogenated to form N-methyl-alpha-(1,4-endoethylenecyclohexane-cis-dicarboximido)-glutarimide, melting point 160°–161° C.

EXAMPLE 25

The 1,4endoxocyclohexane-2,3-exo-cis-dicarboximido-glutaric anhydride obtained by the procedure of example 11 was reacted with methylamine hydrochloride by the procedure of example 23. N-methyl-alpha-(1,4-endoxocyclohexane-2,3-exo-cis-dicarboximido)-glutarimide, melting point 290°–293° C.

EXAMPLE 26

Forty grams of DL-aspartic acid and 55 grams of 1,4endo-ethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboxylic anhydride were reacted using the procedure of example 1. Yield: 67 grams 1,4-endoethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido-succinic anhydride, melting point 212°–213° C.

$C_{14}H_{13}NO_5$ (275.25): Calculated 5.09 percent N, found 4.97 percent N.

The above product was reacted by the procedure of example 1 with urea to form 1,4-endoethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidosuccinimide, melting point 207°–208° C.

The last-mentioned compound was hydrogenated to form 1,4-endoethylenecyclohexane-2,3-cis-dicarboximidosuccinimide, melting point 234°–235° C.

EXAMPLE 27

26.6 grams of DL-aspartic acid and 33 grams of 1,4-endomethylene-Δ^5-cyclohexene-2,3-exo-cis-dicarboxylic anhydride were reacted using the procedure of example 2 to form 1,4-endomethylene-Δ^5-cyclohexene-2,3-exo-cis-dicarboximidosuccinic anhydride, melting point 195°–196° C.

$C_{13}H_{11}NO_5$ (261.23): Calculated 5.36 percent N, found 5.37 percent N.

The above product was transformed by the procedure of example 2 into 1,4-endomethylene-Δ^5-cyclohexene-2,3-exo-cis-dicarboximidosuccinimide, melting point 180°–182° C.

The above compound was hydrogenated to form 1,4-endomethylenecyclohexane-2,3-exo-cis-dicarboximidosuccinimide, melting point 200°–202° C.

EXAMPLE 28

Twenty-five grams of DL-aspartic acid and 31.5 grams of 1,4-endoxocyclohexane-2,3-exo-cis-dicarboxylic anhydride were reacted by the procedure of example 1 to form 1,4-endoxocyclohexane-2,3-exo-cis-dicarboximidosuccinic anhydride. Yield 42 grams, melting point 216°–218° C.

$C_{12}H_{11}NO_6$ (265.22): Calculated 5.28 percent N, found 5.12 percent N.

The above product was reacted with urea to form 1,4-endoxocyclohexane-2,3-exo-cis-dicarboximidosuccinimide, melting point 225°–226° C.

EXAMPLE 29

Ten grams of 1,4-endoxomethylene-Δ^5-cyclohexane-2,3-endo-cis-dicarboximidosuccinic anhydride prepared by the procedure of example 2 were kept together with 5 grams of methylamine hydrochloride in a molten state at 170°–180° C. for 1 hour. The cooled mass was washed with water and dissolved in aqueous alcohol, from which N-methyl-alpha-(1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-succinimide was crystallized melting point 135°–136° C.

$C_{14}H_{14}N_2O_4$ (274.27): Calculated 10.22 percent N, found 10.32 percent N.

The above product was hydrogenated to form N-methyl-alpha-(1,4-endomethylenecyclohexane-2,3endo-cis-dicarboximido)-succinimide, melting point 138–139° C.

$C_{14}H_{16}N_2O_4$(276.29): Calculated 10.14 percent N, found 10.15 percent N.

EXAMPLE 30

1,4-endoethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidosuccinic anhydride prepared by the procedure of example 26 was transformed into N-methyl-alpha-(1,4-endoethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximido)-succinimide by a procedure which is analogous to that of example 29. Melting point 188°–190° C.

$C_{15}H_{16}N_2O_4$ (288.29): Calculated 9.72 percent N, found 9.75 percent N.

The above product was hydrogenated to form N-methyl-alpha-(1,4-endoethylenecyclohexane-2,3-endo-cis-dicarboximido)-succinimide, melting point 155° C.

$C_{15}H_{18}N_2O_4$ (290.31): Calculated 9.65 percent N, found 9.59 percent N.

EXAMPLE 31

1,4-endoxocyclohexane-2,3-exo-cis-dicarboximido-succinic anhydride prepared by the procedure of example 28 was transformed into N-methyl-alpha-(1,4-endoxocyclohexane-2,3-exo-cis-dicarboximido)-succinimide by a procedure which is analogous to that of example 29. Melting point 320° C.

$C_{13}H_{14}N_2O_5$ (278.26): Calculated 10.07 percent N, found 9.96 percent N.

EXAMPLE 32

Thirty grams of L-glutamic acid and 36 grams of 2-exomethyl-1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboxylic anhydride (adduct of citraconic anhydride and cyclopentadiene) were reacted and process by the procedure of example 1 to form 2-exomethyl-1,4-endomethylene-$\Delta_5$cyclohexene-2,3-endo-cis-dicarboximidoglutaric anhydride, melting point 204°–205° C.

$C_{15}H_{15}NO_5$ (289.28): Calculated 4.84 percent N, found 5.15 percent N.

The above product was transformed by the procedure of example 1 into 2-exomethyl-1,4-endomethylene-Δ^5-cyclohexene-2,3-endo-cis-dicarboximidoglutarimide, melting point 210° C.

Hydrogenation resulted in 2-exomethyl-1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboximidoglutarimide, melting point 173° C.

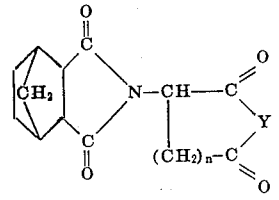
$C_{15}H_{18}N_2O_4$ (290.31): Calculated 9.65 percent N, found 9.55 percent N.

In an analogous procedure, 2exomethyl-1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboxylic anhydride was transformed into 2-exomethyl-1,4-endomethylenecyclohexane-2,3-endo-cis-dicarboximidoglutaric anhydride, melting point 165° C.

$C_{15}H_{17}NO_5$(291.30): Calculated 4.80 percent N, found 5.12 percent N.

What is claimed is:

1. A compound of the formula:



wherein Y is

R is hydrogen or a lower alkyl group, and *n* is 2.

2. A compound as claimed in claim 1 which is 1,4-endomethylene-cyclohexane-2,3-endo-cis-dicarboximidoglutarimide.

3. A compound as claimed in claim 1 which is N-methyl-alpha-(1,4-endomethylene-cyclohexane-2,3-endo-cis-dicarboximido)-glutarimide.

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