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3,551,419

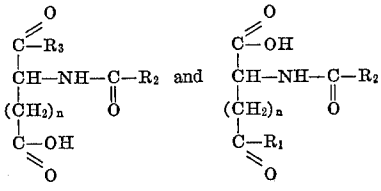
AMINO ACID AMIDES AND PROCESS FOR THEIR PRODUCTION

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Int. Cl. C07d 87/42
U.S. Cl. 260—247.2 14 Claims

ABSTRACT OF THE DISCLOSURE

Compounds having the following formula:



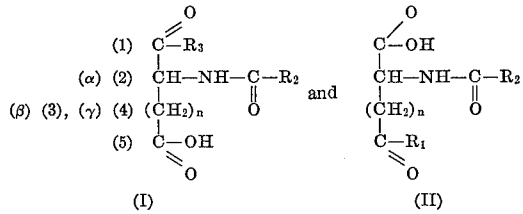
wherein:

R_2 is either phenyl or benzyl;
n is either 1 or 2;
R_1 and R_3 may be:

(a) mono- and di-substituted amino-groups in which the substituent may be:
  (i) linear and branched chain alkyl radicals containing from 3 to 17 carbon atoms when n is 2;
  (ii) linear and branched chain alkyl radicals having from 1 to 17 carbon atoms when n is 1; and
  (iii) a carboalkoxy-substituted phenyl group;
(b) a heterocyclic group which is a morpholino-, piperidino-, pyrrolindino-, 4-antipyrilamino- and hexamethyleneimino radicals;
(c) a benzolamino radical when n is 1.

The above compounds exert either a depressing or stimulating effect on the central nervous system, and are particularly effective as anti-secretory agents in the gastrointestinal tract of warm-blooded mammals. Numerous examples of environments wherein the compounds of the present invention find utility are disclosed in the specification.

This invention relates to certain novel derivatives of N-acyl glutamine and N-acyl isoglutamine and of N-acyl asparagine and N-acyl isoasparagine of the following formula:



(I) (II)

in which R_2 is an alkyl or aryl group as hereinafter described, n is 1 or 2 and R_1 and R_3 are a mono- or di-substituted amino group as hereinafter described. Those compounds where n is 1 are derivatives of aspartic acid and where n is 2 the compounds are derivatives of glutamic acid. The nomenclature for identifying the several carbon atoms is indicated in the above formulas, being the same for both, the compounds of the Formula I being commonly designated the iso-form of said compounds. The compounds I and II may also be identified as derivatives of glutaramic acid and in such case the carboxylic carbon is designated 1 and the amidated carbon designated 5 with the acylamino substituent being on either carbon 2 or 4 in the different isomeric forms.

The foregoing compounds exhibit interesting pharmacological activity and, depending upon the particular substituents present, can exert either a depressant or stimulant effect on the central nervous system. They are particularly effective as anti-secretory agents in the gastrointestinal tract of warm-blooded mammals and also exhibit a protective and trophic or healing action on the mucosa in experimental ulcers in laboratory animals. For example, they are found also to have a protective action on the gastric mucosa where high doses of salicylates or steroids are administered. This effective antisecretory activity makes them particularly useful for the treatment of conditions arising out of gastric hypersecretion. One such use, for example, is the treatment of peptic ulcer in humans.

This invention will be more particularly described in connection with certain glutamic acid derivatives.

Amines useful in forming the novel glutamic compounds of this invention containing said R_1 or R_3 amino substituents are the straight or branched chain primary or secondary aliphatic amines having from 1 to 6 carbon atoms in the longest alkyl radical, which may be the same or different in the case of the secondary amines. These primary and secondary aliphatic amines include, for example, methylamine, dimethylamine, methylethylamine, ethylamine, diethylamine, n-propylamine, isopropylamine, di-isopropylamine, di-n-propylamine, ethyl-n-propylamine, methyl-n-propylamine, n-butylamine, di-n-butylamine, methyl-n-butylamine and the like. Cycloalkyl amines such as hexamethyleneimine and pentamethyleneimine are also useful.

Hydrazine and the mono or symmetrical 1,1-dialkyl substituted hydrazines are also useful amines where the alkyl group contains 1 to 6 carbon atoms.

Suitable hydrazine compounds are, for example, 1,1-dimethylhydrazine, isopropylhydrazine, methylhydrazine, ethylhydrazine, n-propylhydrazine, 1,1-diethylhydrazine and 1,1-di-n-propylhydrazine. The alkaryl substituted hydrazines containing a phenyl, benzyl or phenylethyl substituent can also be employed. While the reaction with hydrazines forms hydrazides these compounds are structurally similar to the amides.

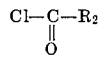
The amines employed may be alkaryl amines such as benzyl amine or β-phenylethylamine, β-phenylpropylamine or β-phenylisopropylamine, or they may include aryl amines such as aniline or o-, m- or p-substituted aniline in which the substituent is halogen such as chlorine or bromine, alkoxy such as ethoxy or methoxy, or in the case of p-aminobenzoic acid the substituent is an esterified carboxy group esterified by an aliphatic alcohol containing 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl and the like, or a mixed alkyl and aryl amine such as methylphenylamine, phenylisopropylamine or phenylpropylamine. Heterocyclic amines may also be substituted in the compounds described and these include, for example, piperidine, morpholine and pyrrolidine. Amino-substituted heterocyclic amines such as 2-aminopyridine, 4-aminopyridine, 2-aminopyrimidine and 4-aminoantipyrine also come within the scope of this invention as substituents in forming said novel glutamic acid amides as do the lower alkyl esters and alkaryl esters of amino acids such as glycine and alanine of the several known isomeric forms, including their methyl, ethyl, propyl, isopropyl and benzyl esters and the amino sugars such as D-glucosamine, D-galactosamine and D-mannosamine.

In use these compounds either alone or in combination with an inert pharmaceutical carrier are formulated into dosage forms such as powders, capsules, tablets, suspen-

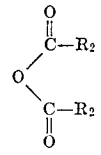
sions, solutions, parenterals, suppositories, and the like and can be administered orally or parenterally or intramuscularly, the active ingredient being present in an amount of from about 50 mg. to 1000 mg. per dose. When administered parenterally or intramuscularly a soluble salt of the acid is employed, for example the sodium or other water soluble alkali metal other non-toxic pharmaceutically acceptable salt may be employed.

In treatment of peptic ulcers, for example, a dose of 50 mg. to 1000 mg. several times daily is recommended. These compounds may also be combined with other therapeutical agents, for example, spasmolytics such as the opium or belladonna alkaloids; parasympatholytics such as tridihexethyl iodide; anticholinergics such as propantheline bromide; antacids such as aluminum, magnesium or calcium hydroxide and magnesium trisilicate; tranquilizers such as the 1,4-benzodiazepines, meprobamate and the like to enhance and broaden their therapeutic spectrum.

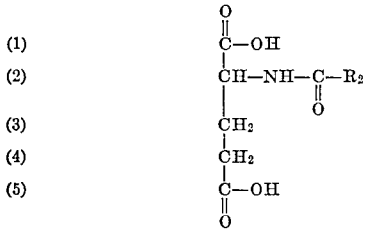
The compounds of this invention may be prepared by reacting an appropriate amino acid such as glutamic acid, for example, with an acyl halide



or an anhydride,

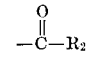


effecting the reaction at a temperature of 0° to 15° C. to yield the N-acylated intermediate:



In the acid chloride or anhydride, R_2 may be a straight or branched chain alkyl group having from 1 to 17 carbon atoms or an aryl group such as phenyl or an o-, m- or p-substituted phenyl group wherein the substituent may be halogen such as chloro or bromo or an alkoxy such as methoxy or ethoxy. If the phthalic anhydride is the anhydride employed for said N-acylation, the product formed is the phthalimido-substituted glutamic acid precursor of the anhydride of Example 10.

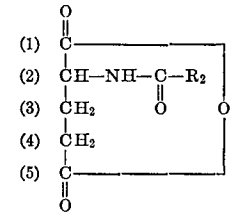
Thus, in the N-acylated intermediates described above the substituent



may be an acyl group such as, for example, benzoyl, acetyl, propionyl, valeryl, isovaleryl, methylethylacetyl, trimethylacetyl, n-caproyl, n-heptoyl, n-butyryl, isobutyryl, n-octoyl, pelargonyl, decanoyl, palmitoyl, stearoyl, phenylacetyl, diphenylacetyl, phthaloyl, p-toluensulfonyl, furoyl, nicotinoyl, isonicotinoyl, beta-phenylpropionyl, beta,beta-diphenylpropionyl and alpha-phenylpropionyl. As described, in the case of phthalic acid the N-acylated intermediate obtained will be a phthalimido compound. Pharmacologically, the preferred compounds are those wherein the substituted N-acylated group is substituted by a benzoyl radical or a phenylacetyl radical.

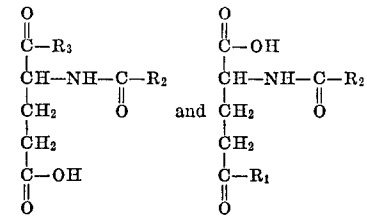
On subsequently reacting the above-described N-acylated intermediates with an acid anhydride such as acetic

anhydride the acylated intermediate is converted to an inner anhydride of the formula:



The formation of said inner anhydride may also be effected with benzoic anhydride or phthalic acid anhydride, for example, but the use of acetic anhydride is most feasible economically. Conveniently, the reaction by which the inner anhydride is formed may be carried out at a temperature of 20° to 30° C.

By reacting the inner anhydride above with the desired primary or secondary amine, usually at a temperature of −7° to 10° C., the inner anhydride is opened and the desired glutamic acide amide is obtained. Since glutamic acid has two carboxyl groups one attached to carbon (2) and the other to carbon (4), the amide substitution can take place at either carboxyl group thus giving rise to an isomeric mixture of the two different amides which correspond respectively to the folowing structures:



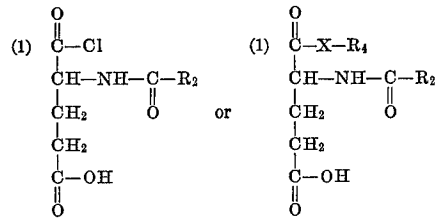
These isomers may be resolved by dissolving the mixture in an aqueous solution of sodium carbonate and then fractionally precipitating the respective isomers by the gradual addition of hydrochloric acid. The isomers are formed in different proportion or ratio depending upon the nature of the solvent in which the reaction is carried out and the particular amine reacted with the inner anhydride to form the amide.

In a particular case, such as where R_2 is phenyl, the isomer formed when one reacts the inner anhydride with a weak amine and thus opens the ring, will tend strongly to favor amide substitution on carbon (1). With a strong amine the substitution is primarily on carbon (5). The use of an acqueous reaction medium in this case also tends strongly to favor the amide substitution on carbon (1) to the almost total exclusion of any amide substitution on carbon (5).

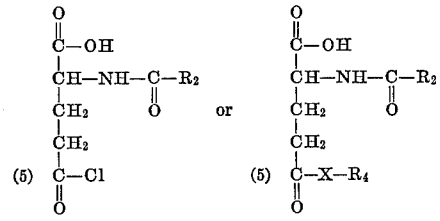
The different isomers formed can be distinguished when heated in a mixture of acetic anhydride and pyridine (see King and McMillan, J.A.C.S. 74, 5202, 1952). Carbon dioxide is readily evolved from the isomer where the unsubstituted carboxyl group is adjacent to the acylamino group, i.e., carbon (2). Where the amide substituent is on carbon (1), heating this isomer in acetic anhydride and pyridine produces little or no evolved carbon dioxide by decarboxylation, or only with difficulty. The isomers can also be distingulished by paper chromatography.

To avoid formation of a mixture of isomers requiring separation or resolution and to form only a particular isomer, the desired acylamino glutamic acid chloride or acylamino glutamic acid ester can be reacted with the de-

sired amine. For example, by reacting the desired amine with the following intermediates:

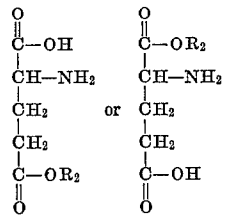


where X is oxygen or sulfur and R_4 is phenyl, vinyl, methyl, benzyl, cyanomethyl or p-nitrophenyl, for example, only the isomer I is formed since amination will take place only at carbon (1). In order to obtain isomer II to the exclusion of isomer I either of the following intermediates can be reacted with the desired amine:

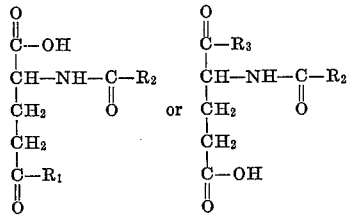


and amination will occur only at carbon (5).

Alternatively, the latter compounds may be obtained by acylating the amino group of a glutamic acid ester of the formula:

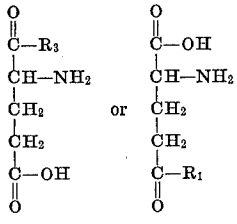


by the Schotten-Baumann reaction with an acyl halide and then reacting the resulting intermediate with the desired amine to produce a substituted glutamic acid amide of the formula:



When the D- or L-forms of the above compounds are employed they remain stereospecific and no racemization occurs.

Additionally to eliminate the problem of forming isomers, one can also react intermediates of the formula:



with an acylating agent to acylate the amino group on carbon (2). Since only one compound will be formed during the acylation of the free amino group, no problem of separating isomers arises.

In addition to effecting separation of said isomers by acidification certain of the isomeric mixtures formed can be separated by fractional crystallization.

Glutamic acid occurs as the naturally occurring dextrorotatory L-form, as the synthetic racemic DL-mixture of these active forms and as the D-form. All of these forms of glutamic acid when converted to the novel glutamic acid amide derivatives of this invention are of desirable activity. Accordingly, when glutamic acid is referred to herein, or aspartic acid as well, it is to be understood as encompassing each of these forms except where a particular form is specifically noted.

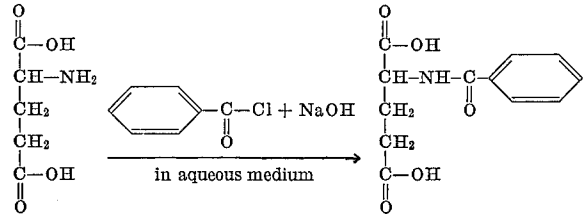
In general, although the glutamic acid initially employed may be the dextrorotatory L-form or the D-form, after acylation and on conversion of the N-acyl compound to the inner anhydride, racemization to the DL-form will commonly occur. Thus, the reaction of the DL-inner anhydride formed yields the DL-form on reaction with the desired primary or secondary amine, as described. However, on converting 2-phthalimido-L-aspartic acid or 2-phthalimido-L-glutaric acid to the anhydride, one can obtain the L-form or, by modifying the conditions, the DL-form.

With 2-acetamino-L-aspartic acid anhydride partial racemization occurs.

The latter two processes lead to one of the two isomers which means that they are specific to one of them only; in addition they are stereospecific which means that during intermediate stages no change occurs in the configuration of the initial starting compound, and no racemization takes place, so that by using these processes the optically active levorotatory forms can be obtained.

The following examples are included in order further to illustrate the invention.

EXAMPLE 1

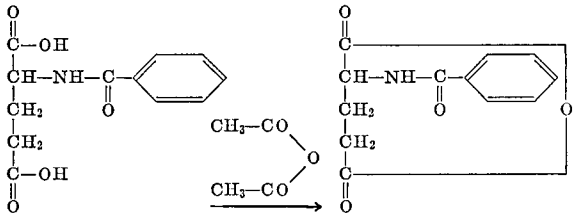


588 g. L (+) glutamic acid [commercial grade, M.P. 247°–249° C. (dec.) $[\alpha]_D^{22}=31°.4$ (1% solution in 6 N HCl)] are gradually added, in small portions, while stirring, to 2400 ml. 2 N NaOH, in such a manner that the internal temperature does not exceed 5° C. employing external cooling with ice or brine.

When all the glutamic acid has been added and is dissolved there is added to the reaction mixture under continued stirring and in such a manner that the internal temperature does not exceed 15° C., 471 ml. benzoylchloride and 1600 ml. 3 N NaOH from two separatory funnels, the addition being made in the following manner: add at once 94.2 ml. benzoylchloride, then dropwise 160 ml. 3 N NaOH (from the other funnel), the speed of addition is regulated so that the pH of the mixture does not exceed 8 (universal indicator paper) and the temperature does not exceed 15° C. When the 160 ml. of the 3 N NaOH solution have all been added, add 47.1 ml. benzoylchloride, then slowly add 160 ml. 3 N NaOH, again add 47.1 ml. of benzoylchloride, followed by the dropwise addition of the same volume of 3 N NaOH solution. This procedure of alternate addition is continued until the benzoylchloride and 3 N NaOH solution have all been added. At this point one adds an additional 1125 ml. of the 3 N NaOH solution at a speed which keeps the temperature below 15° C. and the pH under 8, using universal indicator paper for testing the pH. When all has been added, including the last addition of NaOH, stirring is continued for an additional 30 minutes. The reaction mixture is then acidified, dropwise, with concentrated HCl until Congo Red paper turns blue. The acid solution is stirred for 5 additional minutes, then transferred to a suitable container and stored for 10–18 hours at +5° C. The solids are filtered, re-

pulped in a mortar with 600 ml. ice water and filtered again. The solids are washed on the filter with 400 ml. ice water and pressed dry. The material is then spread out in a thin layer and dried in the air to obtain 2-benzoylamino glutamic acid, M.P. 136°–140° C.

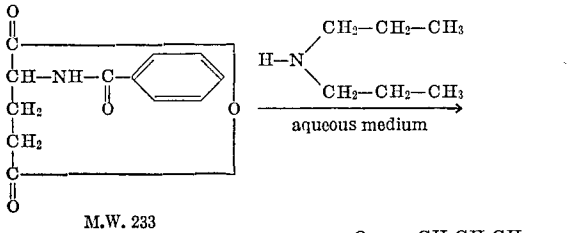
EXAMPLE 2



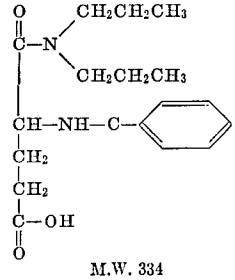
M.W. 251 M.W. 233

1500 g. of 2-benzoylaminoglutamic acid, obtained as in Example 1, are added under stirring to 6 liters of acetic anhydride, previously placed in a flask, equipped with a reflux condenser and a stirrer. The stirred mixture is maintained at room temperature for 8 hours without cooling bath and let stand overnight at room temperature. The reaction mixture is filtered, pressed dry, then dried in an air current for one hour at 60°–70° C., and one hour at 100° C. to obtain 2-benzoylaminoglutamic acid anhydride. Yield: 850 g.=61%.

EXAMPLE 3



M.W. 233

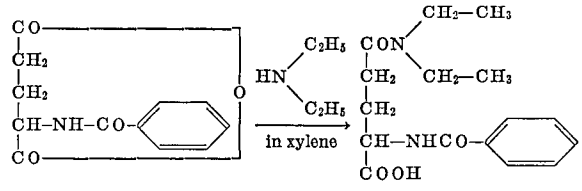


M.W. 334

To an aqueous solution of di-n-propylamine (334 ml. of amine in sufficient water to yield 1400 ml. aqueous solution), are added over a period of 60–75 minutes, under efficient stirring and with cooling to −3° C., 312 g. of 2-benzoylaminoglutamic acid anhydride in such a manner that the temperature remains between −2° and −4° C. When the addition is completed, stirring is continued for 10–15 minutes at −3° C. and 650 cc. glacial acetic acid are added. The temperature is allowed to rise to 6° C. The stirring is continued for 60–80 minutes. The reactant mixture is seeded by adding 2–3 g. of previously prepared 2-benzamido-N,N-dipropylisoglutaramic acid which initiates precipitation of the desired product. The product is product is purified by dissolving the crude material in 20 times by weight of water and adding a stoichiometric amount of $NaHCO_3$ or a slight excess at 60°–70° C. The mixture is acidified with 20% acetic acid with vigorous stirring at room temperature to obtain a pH of 5.5. The stirring is continued for an additional 10–15 minutes, the product 2-benzamido-N,N-dipropylisoglutaramic acid is filtered, washed with stirring with 700 cc. of water for 15 minutes, filtered again and dried in air current at 25° C. to constant weight. Yield 140 gm. M.P. 142–45° C.

EXAMPLE 4

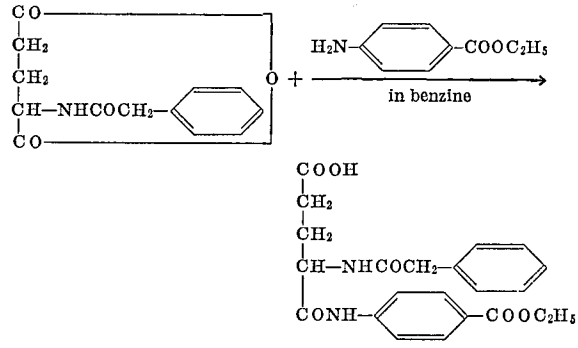
2-benzamindo-N,N-diethyl-DL-glutaramic acid



600 g. of N-benzoylamino-DL-glutaric acid anhydride are added during a period of one hour to 320 cc. of diethylamine, dissolved in 3500 cc. of xylene under stirring and external cooling so that the temperature remains between −7° and −4° C. during the addition. The temperature is then raised to 0° C. and stirring is continued for 14 hours at this temperature. The xylene is decanted, 3 liters of water are added, the remaining xylene is separated by means of a separatory funnel and the acqueous phase is acidified, using Congo Red as the indicator, with acqueous HCl 1:1 under continued stirring at a temperature between 0° and 5° C. The product is filtered, washed under stirring with 2 liters of water and dried to a constant weight at 40° C.; after two crystallizations from acetic acid-water in a proportion of 1:1 there are obtained 375 g. of the desired product melting at 178°–180° C. The product can also be called N-benzoyl-DL-glutamic acid-(5)-di-ethyl amide.

EXAMPLE 5

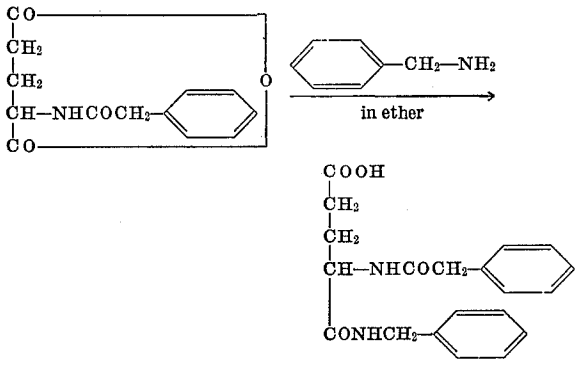
2-phenylacetamindo-N-(p-carbethoxy)-phenylamino-DL-isoglutaramic acid



25 g. of 2-phenylacetamindo-DL-glutaric acid anhydride are dissolved in 200 cc. of benzene and to this solution are added 35 g. of ethyl-p-aminobenzoate dissolved in 200 cc. of benzene and the resulting solution is shaken for 3–4 minutes and then allowed to stand at room temperature overnight. The compound formed is filtered, washed with 200 cc. of refluxing ethyl ether under agitation for 30 minutes, then filtered and crystallized from 100–120 cc. of alcohol. The yield is 25 grams of the above compound, M.P. 156°–158° C. This compound can also be called N-phenylacetyl-DL-glutamic acid-(1)-p-carbethoxyphenylamide.

EXAMPLE 6

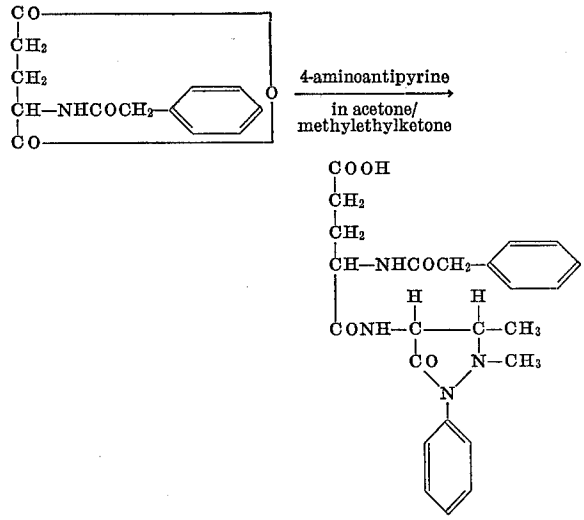
2-phenylacetamido-N-benzylamino-DL-isoglutaramic acid



25 g. of 2-phenylacetamido-DL-glutaric acid anhydride are added over a period of ½ hour to a solution of 22 cc. of benzylamine containing 110 cc. of ether under stirring and cooled so that the temperature remains between +5 and +6° C. Stirring is continued for 15–20 minutes, the mixture filtered and the residue then dissolved in 120 cc. of water which is acidified while stirring by addition of aqueous hydrochloride acid 1:1 (using Congo Red as the indicator), the addition being made so that the temperature will not go above +5° C. The product is filtered, washed under agitation with 100 cc. of water for ten minutes and filtered again. The product obtained is then extracted with 300 cc. of boiling water for 3–4 minutes and filtered. The undissolved portion is extracted twice, the filtrates combined and then cooled at 0° C. to effect crystallization, with 14 g. of the desired product, melting at 149°–151° C. being obtained. This product can also be called N-phenylacetyl-DL-glutamic acid-(1)-benzyl-amide.

EXAMPLE 7

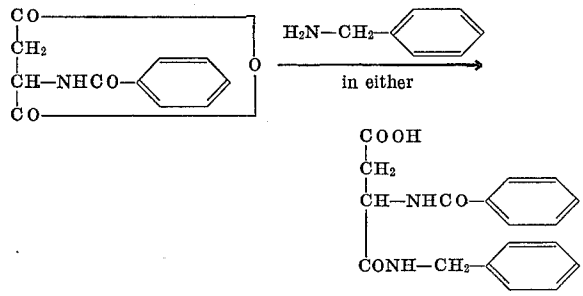
2-phenylacetamido-N-antipyrilamino-DL-isoglutaramic acid



25 g. of 2-phenylacetamido-DL-glutaric acid anhydride (or N-phenacetyl-DL-glutamic acid anhydride) dissolved in 150 cc. of acetone are added to 40 g. of 4-amino-antipyrine dissolved in 150 cc. of methylethylketone at a temperature of 60° C. The solution obtained is allowed to stand at room temperature overnight. The solution is then filtered and washed with 100 cc. of acetone under stirring for 10 minutes and the product obtained then crystallized from alcohol. A yield of 18 g. is obtained, M.P. 130°–133° C.

EXAMPLE 8

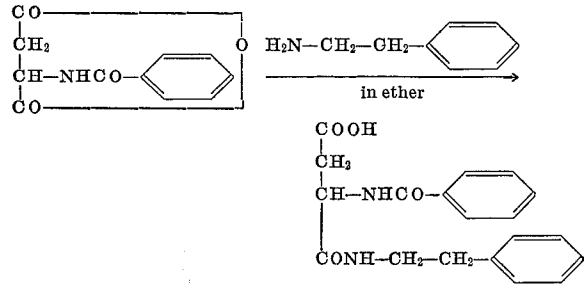
2-benzamido-N-benzylamino-DL-isosuccinamic acid



22 g. of N-benzoyl-DL-aspartic acid anhydride are added to 22 cc. of benzylamine dissolved in 150 cc. of ether under stirring and external cooling regulating the addition so that the temperature does not go above —5° C., the temperature range during the reaction being —8° to 5° C. After the addition stirring is continued for 1 hour and the product formed is filtered off and suspended in 250 cc. of 2 N hydrochloric acid, stirred for 15 minutes, filtered, washed while stirring with 100 cc. of water at 90° C. for 10 minutes, filtered and dried to a constant weight at 50° C. The product yield is 14 g., M.P. 146°–148° C.

EXAMPLE 9

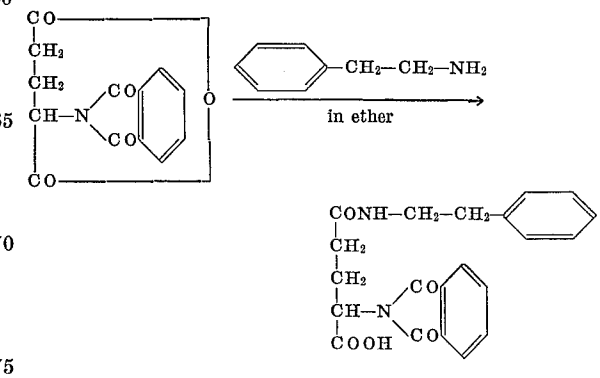
2-benzamido-N-(β)phenylethylamino-DL-isosuccinamic acid



22 g. of N-benzoyl - DL - aspartic acid anhydride are added to 25 cc. of β-phenylethylamine dissolved in 120 cc. of ether under agitation and external cooling while regulating the rate of addition so that the temperature will not go above —5° C., the temperature maintained during the reaction being from —7° to —5° C. Agitation is continued for 1½ hours, the compound is filtered and suspended in 250 cc. of 2 N hydrochloric acid under agitation for 15 minutes which is then followed by filtration. The product filtered off is washed under agitation with 150 cc. of water for 10 minutes then filtered off and dried in air current at 40° C. The yield of product is 16 g. having of a M.P. of 148°–150° C.

EXAMPLE 10

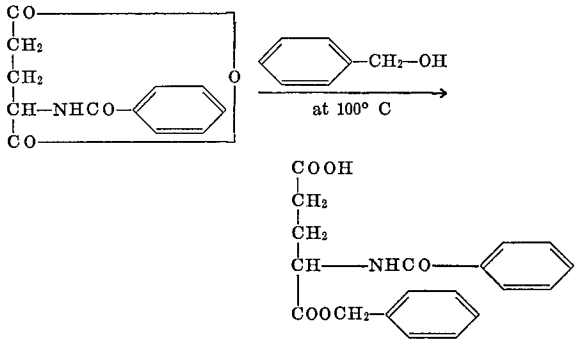
2-phthalimido-N-(β)phenylethylamino-DL-glutaramic acid



25 g. of 2-phthalimido-DL-glutaric acid anhydride are added under agitation over a 15 minute period of 30 cc. of β-phenylethylamine dissolved in 120 cc. of ether under external cooling with running water. The reaction mixture is stirred for 1 hour under reflux, then cooled and filtered. The precipitate obtaind is stirred for 30 minutes with 200 cc. of ether and refiltered. The filtered product is dissolved in 100 cc. of ethylacetate and cooled to 0° C. With caution, a small amount of ether is added and the product which crystallizes from solution filtered, washed with a small amount of boiling water for 2–3 minutes and then dried. Yield 10 g., M.P. 149°–151° C.

EXAMPLE 11

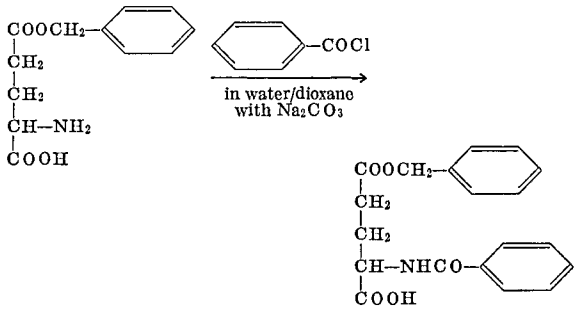
2-benzamido-I-benzyl ester-DL-glutaric acid



80 g. of 2-benzamido-DL-glutaric anhydride and 300 cc. of benzyl alcohol are heated to 100° C. for 4–5 hours under mechanical agitation. The mixture is cooled to room temperature and 400 cc. of ethyl ether are added. The solution so obtained is extracted with an excess of a saturated aqueous solution of sodium bicarbonate. After the extraction, if the pH of the aqueous phase is not less than 7 repeat the extraction twice more. The aqueous extracts are combined and acidified under agitation with 2 N hydrochloric acid, the acid being added drop by drop until the pH is 3, agitation is continued for 2–3 hours, it is filtered and washed under agitation for 10 minutes with 200 cc. of water at 70°–80° C. It is filtered and dried in air current at 50° C. Yield 48 g., M.P. 131–133° C. of the above compound.

EXAMPLE 12

2-benzamido-5-benzylester-L-glutaric acid

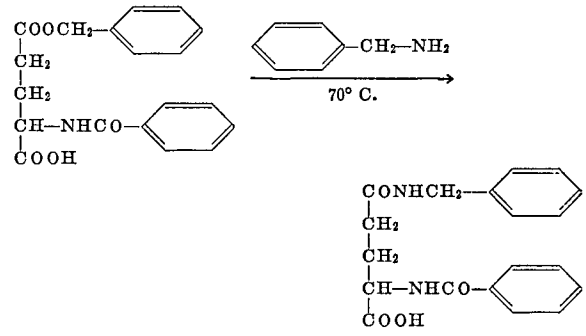


7.11 g. of gamma-L-glutaric acid-benzylester are suspended in 50 cc. of water to which is added 3.18 g. of sodium carbonate. To this suspension at 0° C. are added under agitation 3.5 cc. of benzylchloride dissolved in 20 cc. of dioxane over a period of 1½ hours, agitation is continued for 2 additional hours at 0° C., and there are then added, still under agitation and at 0° C., 0.3 g. of sodium carbonate. Agitation is continued for 15 minutes and the reaction mixture then extracted three times with ethyl ether using 100 cc. for each extraction. The aqueous phase is acidified to Congo red indicator and the acidified

of ethylacetate. The ethylacetate extracts is washed with water, dried over anhydrous sodium sulfate and distilled under vacuum. The residue is recrystallized three times aqueous phase extracted again using three 100 cc. portions from toluene; $[\alpha]_D^{35}=8.95$ (c.=4 in 96% ethanol). M.P.=128–130° C. As a measure of purity, the neutralization equivalent is determined by titration of the carboxylic group with 0.1 N sodium hydroxide against phenolphthalein as indicator.

EXAMPLE 13

2-benzamido-N-benzylamino-L-glutaramic acid



15 g. of 2-benzamido-5-benzylester-L-glutaric acid are warmed with 30–40 cc. of benzylamine at 70° C. for 3 hours and then 100 cc. of water are added under agitation and cooling; acidification is effected by adding HCl drop by drop. The reaction mixtures is filtered and washed with water to a pH of 6–6.5, then dried. After recrystallization from methylisobutylketone there are obtained 9 g. of the above compound melting at 150°–151° C. $[\alpha]_D^{35}=-4.43$ (c.=4 in 96% ethanol). This compound can also be called N-benzoyl-L-glutamic acid-(5)-benzylamide.

EXAMPLE 14

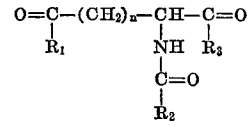
To form an injectable aqueous parenteral composition in the form of a sodium salt, 86 grams of sodium bicarbonate, a slight excess are dissolved in 1000 cc. of water heated to a temperature of 70–80° C. and 334 grams of the compound of Example 3, 2-benzamido-N,N-dipropyl-isoglutaramic acid, are added with stirring and agitation is continued until complete solution, the temperature being maintained between 70 and 75° C. The pH of the solution obtained is adjusted to pH 7.6 by the addition of aqueous 10% sodium bicarbonate. The solution is then put through sterile filtration to eliminate pyrogens, filled into 5 cc. ampouls and the ampouls sterilized at 100° C. for 45 minutes.

Similarly, a parenteral form of the other active antisecretory compounds of this invention may be prepared in similar fashion as the sodium salt.

In addition to the sodium or other alkali metal salts, the alkaline earth metal salts of said compounds may also be prepared as well as their salts with organic bases such as, for example, betaine, choline or diethanolamine.

In addition to the compounds described other compounds have also been prepared in accordance with the procedures described above. The antisecretory activity as well as the LD_{50} in mice (the dosage level which is lethal to half of the test mice) of some of the compounds are given in the table below, the various substitutions of

the groups in the table being made where indicated in the generic formula given:



pletely inhibiting the gastric secretion, this activity is considered to be 100% activity.

TABLE

Compound	n	R_1	R_2—CO—NH	R_3	LD_{50} i.v. in mice (approx.) mg./kg.	Antisecretory activity at a dose of 500 mg./kg.[1]
236 (DL)----	2	—OH	—NHCO—C$_6$H$_5$	—NHCH$_2$—C$_6$H$_5$	2,400	50
239 (DL)----	2	—OH	Same as above----	—N(CH$_2$—CH$_2$)$_2$O	4,000	21
240 (DL)----	2	—OH	----do----	—NH—C$_6$H$_4$—COOC$_2$H$_5$	810	83
242 (DL)----	2	—OH	----do----	—N(CH$_2$—CH$_2$—CH$_3$)$_2$	2,250	55
245 (DL)----	2	—N(CH$_3$)$_2$	----do----	—OH	>2,000	40
246 (DL)----	2	—OH	----do----	—N(CH$_2$—CH$_2$)$_2$CH$_2$	>4,000	8
248 (DL)----	2	—OH	----do----	—N(CH$_2$—CH$_2$)$_2$(CH$_2$)$_2$	2,500	53
249 (DL)----	2	—N(CH$_2$—CH$_3$)$_2$	----do----	—OH	4,000	45
251 (DL)----	2	—N(CH$_2$—CH$_2$)$_2$CH$_2$	----do----	—OH	1,600	59
252 (DL)----	1	—OH	----do----	—NHCH$_2$—C$_6$H$_5$	1,600	51
253 (DL)----	1	—OH	----do----	—N(CH$_2$—CH$_3$)$_2$	3,800	31
279 (DL)----	2	—OH	—NHCOCH$_2$—C$_6$H$_5$	—NH—C$_6$H$_4$—COOC$_2$H$_5$	770	68
282 (DL)----	2	—OH	Same as above----	—NHCH$_2$—C$_6$H$_5$	2,730	N.D.
283 (DL)----	2	—OH	----do----	4-antipirilamino----	5,300	49

[1] No activity=0%; maximum activity=100%.

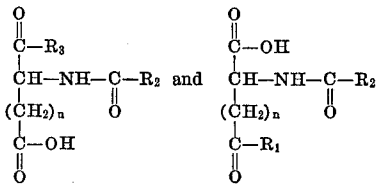
The LD_{50} value in the above table is determined by injecting the test compound into groups containing 10 mice each. The compounds are injected through the tail, each group receiving different dose levels. The lethal dose 50 (LD_{50}) is that dose level which causes death in 50% of the test animals. The antisecretory effect in the above table is determined according to the procedure described by Shay et al., "Gastroenterology" 5:43, 1945. Briefly, pylorus ligation is performed in these rats and at the same time the test compound is given orally via a stomach tube. The gastric contents are collected from each animal 10 hours after treatment. The percent activity is determined on the basis of this gastric secretion test.

An antisecretory effect no different from that observed in the case of the control rats being considered zero activity and where a test compound is capable of com-

It is understood that the foregoing detailed description is given merely by way of illustration and that many variations may be made therein without departing from the spirit of our invention.

Having described our invention, what we desire to secure by Letters Patent is:

1. A compound of the group consisting of compounds of the following formulas:



wherein R_2 is selected from the class consisting of phenyl and benzyl, n is 1 or 2 and R_1 and R_3 are selected from the group consisting of:

(a) mono- and di-substituted amino groups, in which the substituent is a member of the group consisting of:

(i) linear and branched chain alkyl radicals having from 3 to 17 carbon atoms when n is 2;

(ii) linear and branched chain alkyl radicals having from 1 to 17 carbon atoms when n is 1; and

(iii) a p-carboalkoxyphenyl group wherein the alkoxy group contains from 1 to 6 carbon atoms;

(b) a heterocyclic group selected from the class consisting of morpholino-, piperidino-, pyrrolidino-, 4-antipyrilamino- and hexamethyleneimino radicals; and

(c) a benzylamino radical when n is 1.

2. N-benzoyl-DL-glutamic acid-(I)-di-n-propyl amide.

3. N-benzoyl-DL-glutamic acid-(I)-morpholino amide.

4. N - benzoyl-DL-glutamic acid-(I)-(p-carboxyethyl)-phenyl amide.

5. N-benzoyl-DL-glutamic acid-(5)-di-methyl amide.

6. N-benzoyl-DL-glutamic acid-(5)-di-ethyl amide.

7. N-benzoyl-DL-glutamic acid-(I)-hexamethylene amide.

8. N-benzoyl-DL-glumatic acid-(5)-pentamethylene amide.

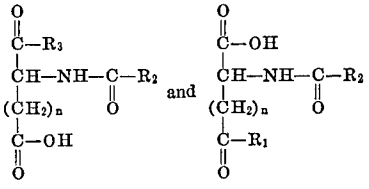
9. N-benzoyl-DL-isoaspartic acid-(I)-benzyl amide.

10. N-benzoyl-DL-isoaspartic acid-(I)-di-ethyl amide.

11. N-phenylacetyl-DL-glutamic acid-(I)-(p-carboxyethyl)-phenyl amide.

12. N-phenylacetyl-DL-glutamic acid-(I)-benzyl amide.

13. A process for preparing a compound of the group consisting of compounds of the following formulas:



wherein R_2 is selected from the class consisting of phenyl and benzyl, n is 1 or 2 and R_1 and R_3 are selected from the group consisting of:

(a) mono- and di-substituted amino groups, in which the substituent is a member of the group consisting of:

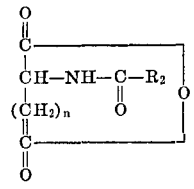
(i) linear and branched chain alkyl radicals having from 3 to 17 carbon atoms when n is 2;

(ii) linear and branched chain alkyl radicals having from 1 to 17 carbon atoms when n is 1; and

(iii) a p-carboalkoxyphenyl group wherein the alkoxy group contains from 1 to 6 carbon atoms;

(b) a heterocyclic group selected from the class consisting of morpholino-, piperidino-, pyrrolidino-, 4-antipyrilamino- and hexamethyleneimino radicals; and

(c) a benzylamino radical when n is 1, said process comprising reacting an inner anhydride of the formula:



with an amine selected from the group consisting of amines of the formula: R_1—H and R_3—H wherein R_1 and R_2, R_3 are as described above, at a temperature of from −7° C. to +10° C.

14. The process of claim 13, wherein the compound is (1) -di-n-propylamide of N-benzoyl-DL-glutamic acid, wherein the inner hydride is 2-benzoylaminoglutamic acid wherein the amine is di-n-propylamine, and wherein the process is conducted in an aqueous medium.

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U.S. Cl. X.R.

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