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Conrow et al.

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[54] **SUBSTITUTED NAPHTHOIC ACIDS**

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[51] **Int. Cl.**[3] **A61K 31/24**; C07C 101/52

[52] **U.S. Cl.** **424/309**; 424/263; 424/285; 424/311; 424/316; 424/319; 560/34; 560/21; 560/45; 560/139; 562/435; 562/439; 562/455; 546/347; 260/346.71; 260/501.11

[58] **Field of Search** 424/309, 263, 285, 311, 424/316, 319; 560/34, 139; 562/439; 546/347; 260/346.71, 501.11

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,123,455	10/1978	Conrow et al.	424/310
4,129,590	12/1978	Conrow et al.	260/507 R

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Assistant Examiner—G. T. Breitenstein

[57] **ABSTRACT**

Certain ureides of substituted naphthoic acids and salts useful as inhibitors of connective tissue destruction.

14 Claims, No Drawings

SUBSTITUTED NAPHTHOIC ACIDS

BACKGROUND OF THE INVENTION

The present invention resides in the concept of certain ureylenebis-[(substituted or unsubstituted-phenylenecarbonylimino)bis-(substituted-naphthoic acids)] and salts thereof which are novel compounds useful as inhibitors of connective tissue destruction.

Abnormal destruction of connective tissue by collagenase and/or neutral proteases causes tissue damage and/or tissue dysfunction. In these conditions an inhibitor of connective tissue destruction acting directly or indirectly would be useful in preventing, retarding, or reversing tissue damage and/or collagen diseases.

The term connective tissue refers to a matrix of at least three protein molecules, collagen, proteoglycan and elastin. These molecules play an important role in the structural integrity of normal tissues. Collagen, the most abundant protein in the body occupies a central position in the connective tissue matrix ["*Biochemistry of Collagen*", Ed. G. N. Ramachandran and A. H. Reddi, Academic Press, New York (1976); P. Bornstein, *Ann. Rev. Biochem.*, 43, 567 (1974); J. Fessler and L. Fessler, *Ann. Rev. Biochem.*, 47, 129 (1978)].

Collagen is, for example, the main structural component of the oral tissue (periodontal ligament, alveolar bone, gingiva, and cementum) [Fullmer, et al., *J. Dental Research,* 48, 646 (1969)]. Collagen amounts to 40% of cartilage protein, 90% of bone protein, and over 90% of dry dermis. Articular cartilage is the resilient tissue that covers the articulating extremities in synovial joints. It consists of collagen fibres that are intimately meshed in a hydrated gel of proteoglycan.

Proteoglycan, as it exists in cartilage, is a molecule in which sulfated polysaccharide chains are covalently linked to a protein backbone ["*Dynamics of Connective Tissue Macromolecules*", Ed. P. M. Burleigh and A. R. Poole, North Holland, Amsterdam (1975)].

Elastin is a major connective tissue component of pulmonary structure ["*Elastin and Elastic Tissue*", Ed. L. B. Sandberg, W. R. Gray, and C. Franzblau, Plenum Press, New York (1977)]. The breakdown of elastin of pulmonary connective tissue is considered the primary event in pulmonary emphysema [A. Janoff in "Proteases and Biological Control", *Cold Spring Harbor Conference on Cell Proliferation,* 2, 603 (1975)].

Degradation of fibrous collagen is initiated by a combination of neutral proteases and tissue collagenase as an integral part of a complex immunopathological process which results in the loss of collagen from normal tissue. Under normal conditions cellular mechanisms maintain a careful balance between the rates of collagen synthesis and degradation. However, in certain pathological conditions, the ensuing elevated levels of neutral proteases and collagenase can result in rapid collagen degradation and tissue dysfunction. For example, in periodontal disease, the generated elevated levels of neutral proteases and collagenase in the gingival crevicular fluid rapidly degrade the fibrous collagen supporting the teeth. Periodontal pockets result ultimately from collagen degradation, and as these pockets deepen, support of tooth is lost and alveolar bone is resorbed [K. Ohlsson, I. Ohlsson, and G. I. Basthall, *Acta Odontol. Scand.*, 32, 51 (1974); L. M. Golub, S. Kenneth, H. McEwan, J. B. Curran, and N. S. Ramamurthy, *J. Dental Research,* 55, 177 (1976); L. M. Golub, J. E. Stakin and D. L. Singer, *J. Dental Research,* 53, 1501 (1974); L. M. Wahl, S. M. Wahl, S. E. Mergenhagen, and G. R. Martin, *Proc. Natl. Acad. Sci. U.S.*, 71, 3598 (1974); *Science,* 187, 261 (1975)].

In arthritic conditions such as in rheumatoid arthritis, septic arthritis, and osteoarthritis elevated degradation of collagen and proteoglycan initiate rapid destruction of articular tissue [J. M. Evanson, J. J. Jefferey, and S. M. Krane, *Science,* 158, 499 (1967); E. D. Harris, D. R. Dibona and S. M. Krane, *J. Clin. Invest.*, 48, 2104 (1969); E. D. Harris, *Rheumatoid Arthritis,* Medcom. Press, N.Y. (1974); Z. Werb, C. L. Mainardi, C. A. Vater and E. D. Harris, *New Eng. J. Med.*, 296, 1017 (1977); J. M. Dayer, R. G. Russell and S. M. Krane, *Science,* 195, 181 (1977); E. D. Harris, C. A. Vater, C. L. Mainardi and Z. Werb, *Agents and Actions,* 8, 35 (1978); D. E. Woolley, E. D. Harris, C. L. Mainardi and C. E. Brinkerhoff, *Science,* 200, 773 (1978); E. D. Harris, C. S. Faulkner, F. E. Brown, *Clin. Orthoped.*, 110, 303 (1975); M. G. Ehrlich, H. J. Mankin, H. Jones, R. Wright and C. Crisper, *J. Bone Jt. Surg.*, 57A, 565 (1975); S. Gordon, W. Newmand and B. Bloom, *Agents and Action,* 8, 19 (1978); "Mechanisms of Tissue Injury With Reference to Rheumatoid Arthritis", Ed. R. J. Perper, *Ann. N.Y. Acad. Sci.*, 256, 1–450 (1975)].

Increased collagen degradation in bone can result in abnormal bone destruction as in osteoporosis [C. G. Griffith, G. Nichols, J. D. Asher and B. Flannagan, *J. Am. Med. Assoc.*, 193, 91 (1965); B. Gardner, H. Gray and G. Hedyati, *Curr. Top. Surg. Res.*, 2, 175 (1970); B. Gardner, S. Wallach, H. Gray and R. K. Baker, *Surg. Forum,* 22, 435 (1971)]. Collagenase activity has also resulted in tissue damage in cholesteatoma [M. Abramson, R. W. Schilling, C. C. Huang and R. G. Salome, *Ann. Otol. Rhinol. Faryngol.*, 81, 158 (1975); M. Abramson and C. C. Huang, *Laryngoscope,* 77, 1 (1976)]. In corneal ulcerations that progress to loss of corneal integrity and function, collagenase has been implicated as a direct factor in corneal destruction [S. I. Brown, C. W. Hook and N. P. Tragakis, *Invest. Ophthamol.*, 11, 149 (1972); M. B. Berman, C. H. Dohlman, P. F. Davison, and M. Ghadinger, *Exptl. Eye Res.*, 11, 225 (1971)]. Elevated levels of collagenase have also been observed in patients with *epidermolysis bullosa,* and a group of related genetic diseases of the skin [E. A. Bauer, T. G. Dahl, and A. Z. Eisen, *J. Invest. Dermatology,* 68, 119 (1977)].

Increased breakdown of elastin of the lung tissue by neutral proteases (elastase) may contribute to the lesions in pulmonary emphysema [I. Mandel, T. V. Darmle, J. A. Frierer, S. Keller and G. M. Turino, *Elastin and Elastic Tissue,* Ed. L. B. Sandberg, W. R. Gray and C. Fransblau, Plenum Press, N.Y., p. 221 (1977)].

A variety of substances, both naturally occurring and synthetically prepared, have been found to be inhibitors of connective tissue destruction, e.g., inhibitors of collagen degradation, that is, as collagenase inhibitors. Such substances include, for example, ethylenediaminetetraacetate, 1,10-phenanthroline, cysteine, dithiothretol and sodium auriothiomalate [D. E. Woolley, R. W. Glanville, D. R. Roberts and J. M. Evanson, *Biochem J.*, 169 265 (1978); S. Seifter and E. Harper, Chap. 18, "The Collagenases" in The Enzymes (3rd Edition), 3, 649–697, Ed. by P. D. Boyer, Academic Press, N.Y. (1971)]. In the eye, a number of studies using collagenase inhibitors directly applied to corneal ulcerations have been reported. Calcium ethylenediaminetetraacetate and acetylcysteine reduce the frequency of ulcer-

ation in the alkali burned rabbit [M. Berman and C. Dohlman, *Arch. Ophthamol.,* 35, 95 (1975)]. Both cysteine and acetylcysteine have been effective in the treatment of acute and chronic corneal ulceration in the human, although the latter compound was preferred because of its greater stability [S. I. Brown, N. P. Tragakis and D. B. Pease, *Am. J. Ophthalmol.,* 74, 316 (1972); M. Berman, *Trace Components of Plasma: Isolation and Clinical Significance,* 7th Annual Red Cross Symposium, p. 225, Alan. R. Liss, Inc., N.Y. (1976)].

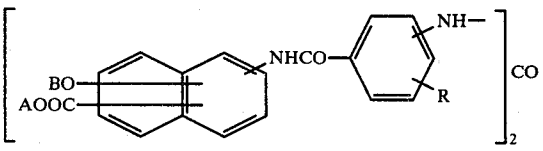
Naturally occurring collagenase inhibitors include the serum components α_2-macroglobulin and β1-anticollagenase [D. E. Woolley, R. W. Glanville, D. R. Roberts and J. M. Evanson, *Biochem. J.,* 169, 265 (1978)].

While some compound may inhibit the destructive effect of collagenase on connective tissue by acting directly on collagenase itself, other compounds may inhibit such destruction by coating, binding or competing with sights on the connective tissue in such a manner as to prevent collagenase from attacking it. The present invention, however, is not to be restricted or limited to any particular mechanism or mode of action. Suffice it to say, that the compounds of this invention have utility as inhibitors of connective tissue destruction albeit in whatever manner or mode.

U.S. Pat. No. 2,687,436 discloses substituted 3-(2-naphthyl)-cyclohexanes useful in the treatment of collagen diseases. British Pat. Nos. 856,357 and 1,246,141 disclose 2-aryl-hexahydro-quinolizines and 1-hydroxyl-praline derivatives, respectively, useful for treating diseases affecting connective tissue. The closest known structurally related compound to those of the present invention and disclosed as having collagenase inhibiting activity is found in *Thromb. Res.,* 10(4), 605–11 (1977), wherein the trypanocidal agent trypan blue is reported as inhibiting the activity of collagenase, or a proteinase contaminant in the collagenase preparation. It is interesting, however, that in this same article, the ureide Suramin is reported as not inhibiting the action of collagenase. The closest known ureides to those of the present invention, and not disclosed as inhibitors of connective tissue destruction or as collagenase inhibitors are those ureides found in *Journal of the Chemical Society,* 3069 (1927), and in U.S. Pat. Nos. 1,218,654 and 1,308,071. The generic disclosure of the '071 patent encompasses a vast number of ureides and with proper selection, among the many possible variables, some of the compounds of this invention may be encompassed within this broad generic disclosure. However, such disclosure by itself does not anticipate or render obvious the invention claimed herein.

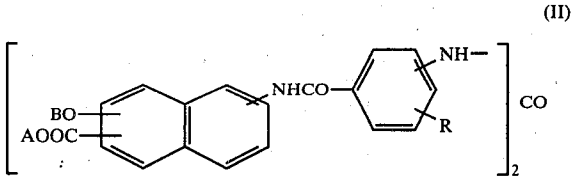
SUMMARY OF THE INVENTION

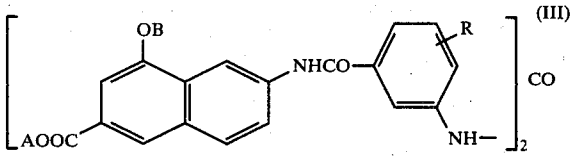
This invention is concerned with novel C-substituted naphthoic acid ureides which may be represented by Formula I:



wherein A is selected from the group consisting of hydrogen, lower (C_1–C_6) alkyl and a pharmaceutically acceptable salt cation; B is selected from the group consisting of hydrogen, lower (C_1–C_6) alkanoyl and a pharmaceutically acceptable salt cation; and R is selected from the group consisting of hydrogen and lower (C_1–C_3) alkyl.

Of particular interest are the group of compounds encompassed within Formula I and illustrated by Formulas II and III:





wherein A, B and R are as defined with reference to Formula I.

By pharmaceutically acceptable salt cation is meant an alkali metal; an alkaline earth metal; ammonium; primary amine, e.g. ethyl amine; secondary amine, e.g. diethylamine or diethanolamine; tertiary amine, e.g. pyridine, triethylamine or 2-dimethylaminomethyl-dibenzofuran; aliphatic amine, e.g. decamethylenediamine; or an aromatic amine.

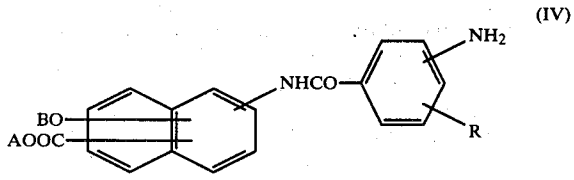
Representative compounds encompassed within this invention include, for example:

6,6′-[Ureylenebis(m-phenylenecarbonylimino)]bis[4-hydroxy-2-naphthoic acid] diethyl ester diacetate

6,6′-[Ureylenebis(m-phenylenecarbonylimino)]bis[4-hydroxy-2-naphthoic acid]

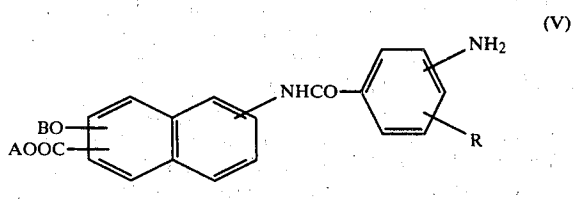
6,6′-Ureylenebis(m-phenylenecarbonylimino)]bis[4-hydroxy-2-naphthoic acid] diethyl ester

This invention is also concerned with C-substituted aminobenzamido naphthoic acids which are intermediates for the preparation of the biologically active compounds of Formula I and which may be represented by Formula IV:



wherein A, B and R are as defined with reference to Formula I.

Of particular interest are the group of intermediate compounds encompassed within Formula IV and illustrated by Formulas V and VI:



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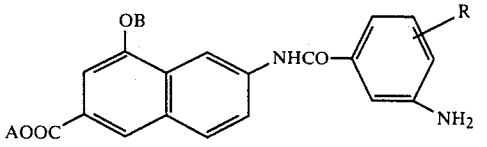
(VI)



wherein A, B and R are as defined with reference to Formula I.

Representative compounds encompassed by Formula IV include, for example:

6-(m-Aminobenzamido)-4-hydroxy-2-naphthoic acid ethyl ester acetate

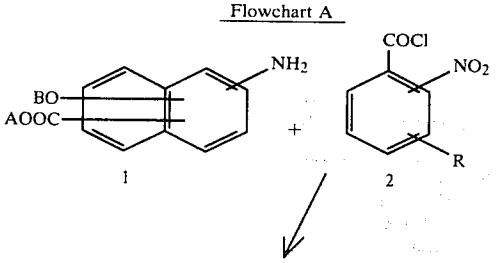
This invention is also concerned with a method of inhibiting connective tissue destruction in a warm-blooded animal which comprises administering to said animal an effective inhibiting amount of a compound encompassed within Formula I. Moreover, this invention is concerned with a method of inhibiting the degradation sequelae of collagenase activity in a body fluid, such as crevicular fluid, synovial fluid and the like, which comprises subjecting body fluid collagenase to the action of an effective collagenase inhibiting amount of a compound encompassed within the above formula. Body fluid can include blood, plasma, serum, synovial fluid, crevicular fluid, ocular fluid, etc., containing collagenase. The method of use aspect of this invention is further concerned with a method of inhibiting the action of collagenase in a warm-blooded animal which comprises internally administering to said animal an effective collagenase inhibiting amount of a compound encompassed within the above formula.

Since the compounds of the present invention find utility as inhibitors of connective tissue destruction or as collagenase inhibitors in body fluids, as such they may be useful in ameliorating or preventing those pathological reactions resulting from the functioning of collagenase, and in the therapeutic treatment of warm-blooded animals having connective tissue disorders such as periodontal diseases and diseases of the teeth, osteoporosis, osteolysis, Paget's disease, hyperparathyroidism of renal failure, rheumatoid arthritis, septic arthritis, osteoarthritis, gout, acute synovitis, scleroderma, psoriasis, epidermolysis bullosa, keloids, blisters, cholesteatoma of the ear, and corneal ulceration. The compounds of the present invention may also be useful in those pathological states where excessive activity of neutral proteases causes tissue damage.

DESCRIPTION OF THE INVENTION

The compounds of the present invention may be prepared according to the following Flowchart A.

Flowchart A



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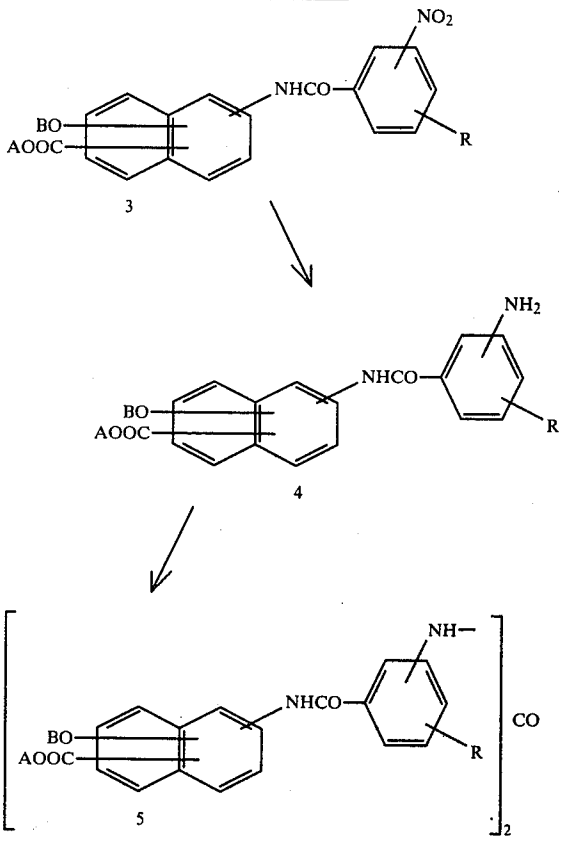
Flowchart A



With reference to Flowchart A, a substituted-aminonaphthoic acid 1 is dissolved in pyridine, cooled and reacted with an excess substituted nitrobenzoylchloride 2, giving a substituted nitrobenzamido-substituted naphthoic acid 3, which is hydrogenated in the presence of a suitable catalyst to give the corresponding amine derivative 4. The amine 4 is dissolved in pyridine and phosgenated to give the final ureide product 5 which is isolated by conventional procedures.

DETAILED DESCRIPTION OF THE INVENTION

The following examples describe in detail the preparation and formulation of representative compounds of the present invention.

EXAMPLE 1

6-(m-Aminobenzamido)-4-hydroxy-2-naphthoic acid, ethyl ester, acetate

A solution of 20 g. or 4-hydroxy-6-nitro-2-naphthoic acid [W. F. Beech and N. Legg, J. Chem. Soc., 1887 (1949)], 385 ml. of absolute ethanol and 20 ml. of concentrated sulfuric acid is refluxed for 4 hours, concentrated and diluted with water. The solid is collected by filtration, washed with water until neutral and crystallized from 250 ml. of acetonitrile, giving 16.5 g. of 4-hydroxy-6-nitro-2-naphthoic acid ethyl ester as yellow crystals.

To a mixture of 22.47 g. of 4-hydroxy-6-nitro-2-naphthoic acid ethyl ester in 150 ml. of pyridine is added 8.5 ml. of acetic anhydride. The mixture is stirred for 5 minutes, warmed on a steam bath until solution is com-

plete and then allowed to stand for 10 minutes. The solution is poured into one liter of ice water and then filtered. The solid is dissolved in 500 ml. of methylene chloride, dried over sodium sulfate, filtered and concentrated to about 200 ml. A 300 ml. portion of ethanol is added and the product is allowed to crystallize, giving 25.1 g. of 4-hydroxy-6-nitro-2-naphthoic acid ethyl ester acetate as pale yellow crystals.

A mixture of 26.3 g. of 4-hydroxy-6-nitro-2-naphthoic acid ethyl ester acetate, 250 ml. of tetrahydrofuran and 2.5 g. of 10% palladium on carbon is hydrogenated on a Parr shaker at 40-20 psi over 45 minutes. The mixture is filtered through diatomaceous earth and evaporated in vacuo to an oil. This oil is crystallized from 200 ml. of ether, giving 21.8 g. of 6-amino-4-hydroxy-2-naphthoic acid ethyl ester acetate as beige crystals.

To a cooled (ice bath) solution of 9.02 g. of 6-amino-4-hydroxy-2-naphthoic acid ethyl ester acetate in 50 ml. of dry pyridine is added 6.74 g. of m-nitrobenzoyl chloride. After 5 minutes the ice bath is removed and stirring is continued at room temperature for 30 minutes. The solution is poured into 500 ml. of water and stirred until the precipitate solidifies. The solid is collected by filtration, washed with water, dried and crystallized from 250 ml. of acetonitrile at 5° C., giving 13.0 g. of 4-hydroxy-6-m-nitrobenzamido-2-naphthoic acid ethyl ester acetate as beige crystals.

A mixture of 13.0 g. of 4-hydroxy-6-m-nitrobenzamido-2-naphthoic acid ethyl ester acetate, 125 ml. of tetrahydrofuran and 1.25 g. of 10% palladium on carbon is hydrogenated in a Parr shaker at 45–37 psi for one hour. The mixture is filtered through diatomaceous earth and the filtrate is evaporated in vacuo to a pale yellow glass. This glass is crystallized by trituration with ether and the solid is recrystallized from 100 ml. of acetonitrile at 5° C., giving 10.35 g. of the desired product as colorless crystals, m.p. 185°–187° C.

EXAMPLE 2

6,6′-[Ureylenebis(m-phenylenecarbonylimino)]bis[4-hydroxy-2-naphthoic acid]diethyl ester diacetate

To a solution of 10.23 g. of 6-(m-aminobenzamido)-4-hydroxy-2-naphthoic acid ethyl ester acetate in 60 ml. of dry pyridine is added a solution of 1.3 g. of phosgene in 5 ml. of dry ethylene glycol, dimethyl ether, dropwise, with stirring and cooling, during 2–3 minutes. Stirring is continued at room temperature for 2 hours, then the solution is poured into 800 ml. of water. The gummy precipitate is triturated with water, giving a red solid. This solid is stirred and refluxed in 300 ml. of ethanol, cooled, filtered and the solid is washed with ethanol, then ether. This solid is dissolved in 120 ml. of hot dimethylformamide, treated with charcoal and filtered through diatomaceous earth. The filtrate is warmed to 80° C. and diluted slowly, with stirring with 60 ml. of water. The mixture is cooled to room temperature and the solid is collected by filtration, washed with 67% aqueous dimethylformamide, ethanol, then ether and dried overnight at 110° C., giving 8.45 g. of the desired product as a pale tan powder, m.p. 285°–287° C.

EXAMPLE 3

6,6′-[Ureylenebis(m-phenylenecarbonylimino)]bis[4-hydroxy-2-naphthoic acid]

To a cooled (water bath) solution of 4.06 g. of 6,6′-[ureylenebis(m-phenylenecarbonylimino)]bis[4-hydroxy-2-naphthoic acid]diethyl ester diacetate in 60 md. of dimethylsulfoxide is added 60 ml. of 2 N sodium hydroxide, portionwise, with stirring, in a nitrogen atmosphere. The mixture is stirred under nitrogen at room temperature for 2 hours, then poured into 300 ml. of water and filtered. The filtrate is acidified to pH 2 with the addition of 10 ml. of concentrated hydrochloric acid and 50 g. of sodium acetate trihydrate are added. The gel is filtered and washed with water, then further washed with water in a centrifuge and dried by co-evaporation with 750 ml. of n-propanol, giving a red-brown powder. This powder is dissolved in 25 ml. of hot dimethylformamide, diluted slowly with 15 ml. of water and cooled in a refrigerator. The precipitate is collected by filtration, washed successively with 8 ml. of 50% aqueous dimethylformamide, ethanol:ether (1:1) and finally ether, then dried overnight at 110° C., giving 1.6 g. of the desired product as a pale tan powder, m.p. 297°–300° C. (dec.).

EXAMPLE 4

6,6′-[Ureylenebis(m-phenylenecarbonylimino)]bis[4-hydroxy-2-naphthoic acid] diethyl ester

To a cooled (water bath) solution of 2.0 g. of 6,6′-[ureylenebis(m-phenylenecarbonylimino)]bis[4-hydroxy-2-naphthoic acid] diethyl ester diacetate in 60 ml. of dimethylformamide is added 40 ml. of 0.25 N sodium hydroxide, dropwise with stirring over 10 minutes. The solution is stirred for an additional 10 minutes, 80 ml. of pyridine is added and the solution is poured with cooling into a mixture of 800 ml. of water and 85 ml. of concentrated hydrochloric acid. The solid is collected by filtration, washed with water and dried at room temperature. This solid is dissolved in hot 2-methoxyethanol at a concentration of 4% (w/v). This solution is then distilled with ½ its volume of water and then cooled to room temperature. The precipitate is collected by filtration and washed with 50% aqueous 2-methoxyethanol, ethanol, then ether. This solid is dissolved in a mixture of 2-methoxyethanol:dimethylformamide (6.5:1) giving an approximate 4% (w/v) solution, diluted with water and filtered. The solid is washed as described above, then with acetone and dried at 110° C., overnight giving 417 mg. of the desired product as a tan powder, m.p. 265°–280° C. (dec.).

EXAMPLE 5

Preparation of Compressed Tablet

Ingredient	mg./Tablet
Active Compound	0.5–500
Dibasic Calcium Phosphate N.F.	qs
Starch U.S.P.	40
Modified Starch	10
Magnesium Stearate U.S.P.	1–5

EXAMPLE 6

Preparation of Compressed Tablet - Sustained Action

Ingredient	mg./Tablet
Active Compound as Aluminum Lake*, Micronized	0.5–500 (as acid equivalent)
Dibasic Calcium Phosphate N.F.	qs
Alginic Acid	20
Starch U.S.P.	35

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