

PATENT SPECIFICATION

NO DRAWINGS

1,106,271

1,106,271



Date of Application and filing Complete Specification: Jan. 5, 1966.
No. 554/66.

Application made in United States of America (No. 427124) on Jan. 21, 1965.
Complete Specification Published: March 13, 1968.

© Crown Copyright 1968.

Index at acceptance: —C2 C(1F1C2, 1F1D2, 2B40C, 2B40J1, 2B40J2, 2B40J3, 2D3, 3A10E1)
Int. Cl.: —C 07 c 125/00

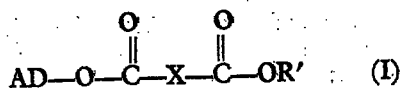
COMPLETE SPECIFICATION

N-Adamantylloxycarbonyl Derivatives of α -Amino Acids and Process for Preparing same

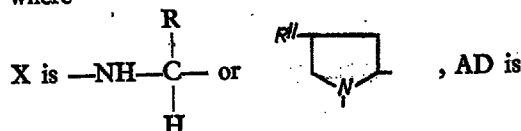
We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 740 South Alabama Street, City of Indianapolis, State of Indiana, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns novel N-adamantylloxycarbonyl derivatives of α -amino acids and a process for preparing these derivatives.

The present invention provides N-adamantylloxycarbonyl derivatives of α -amino acids represented by the following formula



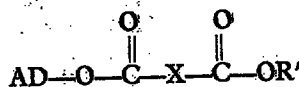
where



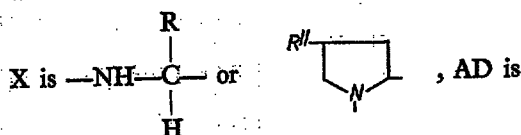
adamantyl, methyladamantyl, dimethyladamantyl or homo-adamantyl; R is hydrogen, C_1-C_4 alkyl, hydroxy-substituted C_1-C_4 alkyl, ~~carbalkoxy~~ (C_1-C_4) -substituted C_1-C_4 alkyl, mercapto-substituted C_1-C_4 alkyl, C_1-C_4 alkylmercapto-substituted C_1-C_4 alkyl, guanidino-substituted C_1-C_4 alkyl, phenyl, benzyl, thienyl, furyl, imidazolyl-methyl, indolylmethyl and hydroxy-indolyl-methyl; R' is hydrogen or C_1-C_4 alkyl; R'' is hydrogen or hydroxyl; and the alkali metal and amine salts thereof.

The present invention also provides a process for the preparation of N-adamantylloxycarbonyl derivatives of α -amino acids represented by the formula:

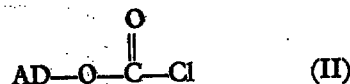
[Price 4s. 6d.]



where



adamantyl, methyladamantyl, dimethyladamantyl or homo-adamantyl; R is hydrogen, C_1-C_4 alkyl, hydroxy-substituted C_1-C_4 alkyl, ~~carbalkoxy~~ (C_1-C_4) -substituted C_1-C_4 alkyl, mercapto-substituted C_1-C_4 alkyl, C_1-C_4 alkylmercapto-substituted C_1-C_4 alkyl, guanidino-substituted C_1-C_4 alkyl, phenyl, benzyl, thienyl, furyl, imidazolyl-methyl, indolylmethyl and hydroxyindolyl-methyl; R' is hydrogen or C_1-C_4 alkyl; R'' is hydrogen or hydroxyl; and the alkali metal and amine salts thereof, which comprises reacting an adamantyl chloroformate represented by the formula



with a compound of the formula



where AD, X and R' are defined as above in a non-acidic inert reaction medium.

The adamantyl chloroformates employed in the process of the present invention can be prepared by the method described in our co-pending divisional application No. 32779/67 (Serial No. 1106272) by reacting a compound represented by the formula

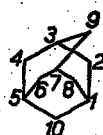
AD—OH (IV)

where AD is defined as above with phosgene in the presence of a tertiary amine in an inert solvent to form an adamantyl chloroformate represented by formula II. The adamantyl chloroformates can be isolated and purified, if desired.

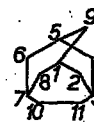
As can readily be seen, the N-adamantyl-oxycarbonyl derivatives of α -amino acids represented by the formula I include derivatives of the naturally occurring α -amino acids, as well as lower homologues and isosteres thereof. Such compounds are useful in the synthesis of peptides, and in the synthesis of certain penicillins and cephalosporins. The adamantyloxycarbonyl group functions as a blocking group, preventing unwanted reactions of the blocked amino group during the course of synthesizing the peptide, penicillin or cephalosporin, as the case may be.

The adamantyloxycarbonyl blocking group can be readily cleaved from the adamantyl-carbamate by treatment with trifluoroacetic acid or with anhydrous hydrogen chloride in an inert solvent such as dioxane or by other known methods.

Adamantane and homo-adamantane, from which are derived the adamantyl, methyl-adamantyl, dimethyladamantyl and homo-adamantyl radicals referred to above, are tricyclic multi-bridged hydrocarbons. Their formulas are conventionally represented as follows:



adamantane

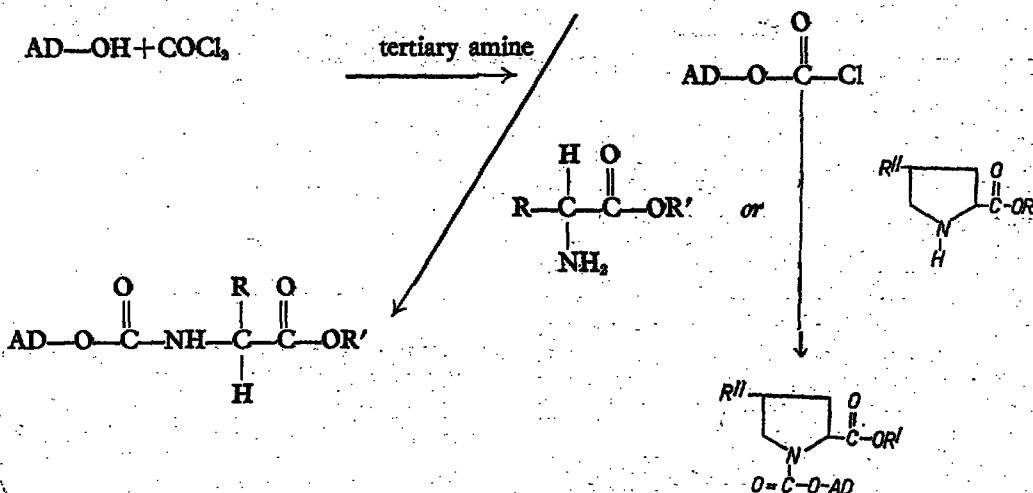


homo-adamantane

In formula I above, when R or R' is C_1-C_4 alkyl, it can be, illustratively, isobutyl, *sec*-butyl, isopropyl, *n*-propyl, methyl, ethyl, *n*-butyl and *t*-butyl. When R is a substituted C_1-C_4 alkyl group, illustrative groups include hydroxymethyl, mercaptomethyl, methylmercaptomethyl, methylmercaptoethyl, ethylmercaptomethyl, γ -guanidinobutyl, β -hydroxyethyl, β -hydroxy-*t*-butyl, β -isopropylmercaptoethyl, γ -hydroxypropyl, γ -mercapto-*n*-butyl, carboxymethyl and β -carboxyethyl. The terms phenyl and benzyl include phenyl and benzyl radicals containing substituents in the phenyl ring, illustrative examples of which include fluoro, chloro, bromo, iodo, lower alkyl, lower alkoxy, hydroxy, and halo-substituted lower alkyl.

Illustrative compounds coming within the scope of this invention include: N - 1 - adamantyloxycarbonyl L-tyrosine, N - 3 - methyladamantyloxycarbonyl L-phenylalanine, N,N' - bis - (1-adamantyloxycarbonyl) L-cystine, N - 3,5 - dimethyladamantyloxycarbonyl D-valine, ethyl N - 3 - homo-adamantyloxycarbonyl 2,4 - dichlorophenylalaninate, N - 1 - adamantyloxycarbonyl 2,6-dimethoxyphenylglycine, and N - 1 - adamantyloxycarbonyl L-proline.

Compounds represented by the above formula are prepared by the following reaction scheme:



wherein AD, R, R' and R'' have the same meaning as herein above. In carrying out the above reaction sequence, 1-hydroxyadamantane or 3 - methyl - 1 - hydroxyadamantane

or 3,5 - dimethyl - 1 - hydroxyadamantane or 3 - hydroxyhomo-adamantane is reacted with phosgene in the presence of tertiary amine such as pyridine, trimethylpyridine, quinoline, or tri-ethylamine in an inert solvent, such as anhydrous benzene or ether or other hydrocarbon or ethereal solvents, to form the corresponding adamantyl chloroformate which can be preserved in a suitable solvent, or can be isolated as a white, crystalline solid.

The preparation of the N-adamantyloxy-carbonyl derivative of the amino acid in which the amino group is to be protected or blocked is effected simply by mixing the adamantyl chloroformate with the amino acid compound in an inert solvent, under slightly alkaline conditions such as are secured by employing a solvent like alcohol or dioxane, and dilute, aqueous sodium hydroxide or other equivalent material as the alkalinizing agent.

This invention is further illustrated by the following specific examples in which Example I describes the preparation of an adamantyl chloroformate which may be employed as a starting material in the method of the present invention and Examples II and III describe the preparation of compounds in accordance with the present invention, employing the product of Example I as a starting material.

EXAMPLE I

A solution containing 20 g. of phosgene in 100 ml. of anhydrous benzene was maintained at about 20°C. by means of an ice-water bath. A mixture containing 8 g. of 1-hydroxyadamantane, 6 g. of pyridine, and 200 ml. of ether was added dropwise with stirring to the phosgene solution over a period of about 1 hour. 100 ml. of anhydrous benzene were then added and the reaction mixture was maintained at ambient temperature for about 1 hour and was then filtered. The filtrate was poured over a mixture of ice and water and the organic layer containing the 1-adamantyl chloroformate was separated and dried. Evaporation of the solution *in vacuo* at room temperature, yielded 1-adamantyl chloroformate as a white crystalline solid melting at about 40—42°C. The material was further purified by recrystallization from anhydrous low-boiling petroleum-ether at -20°C., yielding crystals melting at about 46—47°C.

Adamantyl chloroformate can be stored essentially without decomposition at 4°C. in benzene-ether solution containing a small amount of calcium carbonate as a stabilizer.

EXAMPLE II

A solution of sodium D-phenylglycine was prepared by suspending 151 mg. of D-phenylglycine in a mixture of 2 ml. of water and 1.2 ml. of 1N aqueous sodium hydroxide at

0°C. 225 Mg. of 1-adamantyl chloroformate dissolved in a mixture of 2.5 ml. of dioxane and 1 ml. of ether were added in five portions to the sodium D-phenylglycinate solution over a period of about 40 minutes. During the addition of the acid chloride solution, an additional 1 ml. of 1N aqueous sodium hydroxide was added dropwise in order to maintain a slightly alkaline pH in the reaction mixture. The reaction mixture was extracted with three volumes of ether to remove unreacted adamantyl chloroformate, the alkaline aqueous layer was cooled to about 0°C. and was cautiously acidified with 85% phosphoric acid to about pH 4.5. The milky precipitate of N - 1 - adamantyloxycarbonyl - D - phenylglycine which formed was extracted with ether. The ether solution was separated and dried. Evaporation of the ether *in vacuo* yielded an oily residue which when triturated with a few drops of cyclohexane and cooled to about 0°C. yielded N - 1 - adamantyloxycarbonyl - D - phenylglycine as a white crystalline solid melting at about 119—121°C.

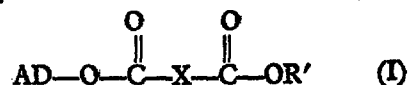
EXAMPLE III

Following the procedure of Example II, 1-adamantyl chloroformate was reacted with sodium glycinate to yield N - 1 - adamantyloxycarbonyl glycine melting at about 141—142.5°C. after recrystallization from hexane.

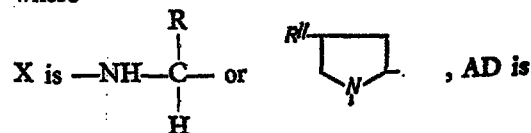
In addition to the amino acids utilized in Examples II and III, other amino acids which can be converted to adamantyloxycarbonyl derivatives by the procedure described, include illustratively, leucine, isoleucine, tyrosine, valine, serine, alanine, phenylalanine, DOPA, norleucine, histidine, diiodotyrosine, arginine, cysteine, methionine, ethionine, proline, hydroxyproline, aspartic acid and glutamic acid.

WHAT WE CLAIM IS:—

1. N-Adamantyloxycarbonyl derivatives of α -amino acids represented by the following formula



where



adamantyl, methyladamantyl, dimethyladamantyl or homo-adamantyl; R is hydrogen, C_1-C_4 alkyl, hydroxy-substituted C_1-C_4 alkyl, carboxy (C_1-C_4)-substituted C_1-C_4 alkyl, mercapto-substituted C_1-C_4 alkyl, C_1-C_4 alkylmercapto-substituted C_1-C_4 alkyl, guanidino-substituted C_1-C_4 alkyl, phenyl, benzyl, thienyl, furyl, imidazolylmethyl, indolylmethyl and hydroxyindolylmethyl; R' is hydrogen or C_1-C_4 alkyl; R''



or 3,5 - dimethyl - 1 - hydroxyadamantane or 3 - hydroxyhomo-adamantane is reacted with phosgene in the presence of tertiary amine such as pyridine, trimethylpyridine, quinoline, or tri-ethylamine in an inert solvent, such as anhydrous benzene or ether or other hydrocarbon or ethereal solvents, to form the corresponding adamantyl chloroformate which can be preserved in a suitable solvent, or can be isolated as a white, crystalline solid.

The preparation of the N-adamantyl-oxycarbonyl derivative of the amino acid in which the amino group is to be protected or blocked is effected simply by mixing the adamantyl chloroformate with the amino acid compound in an inert solvent, under slightly alkaline conditions such as are secured by employing a solvent like alcohol or dioxane, and dilute, aqueous sodium hydroxide or other equivalent material as the alkalinizing agent.

This invention is further illustrated by the following specific examples in which Example I describes the preparation of an adamantyl chloroformate which may be employed as a starting material in the method of the present invention and Examples II and III describe the preparation of compounds in accordance with the present invention, employing the product of Example I as a starting material.

EXAMPLE I

A solution containing 20 g. of phosgene in 100 ml. of anhydrous benzene was maintained at about 20°C. by means of an ice-water bath. A mixture containing 8 g. of 1-hydroxyadamantane, 6 g. of pyridine, and 200 ml. of ether was added dropwise with stirring to the phosgene solution over a period of about 1 hour. 100 ml. of anhydrous benzene were then added and the reaction mixture was maintained at ambient temperature for about 1 hour and was then filtered. The filtrate was poured over a mixture of ice and water and the organic layer containing the 1-adamantyl chloroformate was separated and dried. Evaporation of the solution *in vacuo* at room temperature, yielded 1-adamantyl chloroformate as a white crystalline solid melting at about 40–42°C. The material was further purified by recrystallization from anhydrous low-boiling petroleum-ether at –20°C., yielding crystals melting at about 46–47°C.

Adamantyl chloroformate can be stored essentially without decomposition at 4°C. in benzene-ether solution containing a small amount of calcium carbonate as a stabilizer.

EXAMPLE II

A solution of sodium D-phenylglycine was prepared by suspending 151 mg. of D-phenylglycine in a mixture of 2 ml. of water and 1.2 ml. of 1N aqueous sodium hydroxide at

0°C. 225 Mg. of 1-adamantyl chloroformate dissolved in a mixture of 2.5 ml. of dioxane and 1 ml. of ether were added in five portions to the sodium D-phenylglycinate solution over a period of about 40 minutes. During the addition of the acid chloride solution, an additional 1 ml. of 1N aqueous sodium hydroxide was added dropwise in order to maintain a slightly alkaline pH in the reaction mixture. The reaction mixture was extracted with three volumes of ether to remove unreacted adamantyl chloroformate, the alkaline aqueous layer was cooled to about 0°C. and was cautiously acidified with 85% phosphoric acid to about pH 4.5. The milky precipitate of N - 1 - adamantyloxycarbonyl - D - phenylglycine which formed was extracted with ether. The ether solution was separated and dried. Evaporation of the ether *in vacuo* yielded an oily residue which when triturated with a few drops of cyclohexane and cooled to about 0°C. yielded N - 1 - adamantyloxycarbonyl - D - phenylglycine as a white crystalline solid melting at about 119–121°C.

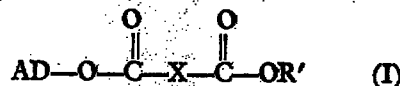
EXAMPLE III

Following the procedure of Example II, 1-adamantyl chloroformate was reacted with sodium glycinate to yield N - 1 - adamantyloxycarbonyl glycine melting at about 141–142.5°C. after recrystallization from hexane.

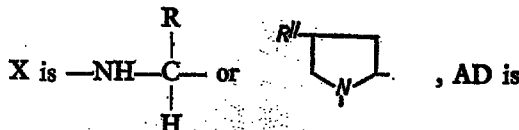
In addition to the amino acids utilized in Examples II and III, other amino acids which can be converted to adamantyloxycarbonyl derivatives by the procedure described, include illustratively, leucine, isoleucine, tyrosine, valine, serine, alanine, phenylalanine, DOPA, norleucine, histidine, diiodotyrosine, arginine, cysteine, methionine, ethionine, proline, hydroxyproline, aspartic acid and glutamic acid.

WHAT WE CLAIM IS:—

1. N-Adamantyloxycarbonyl derivatives of α -amino acids represented by the following formula



where



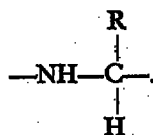
adamantyl, methyladamantyl, dimethyladamantyl or homo-adamantyl; R is hydrogen, C₁–C₄ alkyl, hydroxy-substituted C₁–C₄ alkyl, carbalkoxy (C₁–C₄)-substituted C₁–C₄ alkyl, mercapto-substituted C₁–C₄ alkyl, C₁–C₄ alkylmercapto-substituted C₁–C₄ alkyl, guanidino-substituted C₁–C₄ alkyl, phenyl, benzyl, thienyl, furyl, imidazolylmethyl, indolylmethyl and hydroxyindolylmethyl; R' is hydrogen or C₁–C₄ alkyl; R''

Carbalkoxy

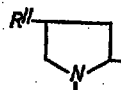


is hydrogen or hydroxyl; and the alkali metal and amine salts thereof.

2. The compound of claim 1 where X is



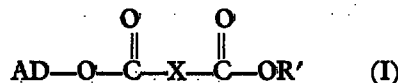
5 3. The compound of claim 1 where X is



4. N - 1 - Adamantylloxycarbonyl glycine.

5. N - 1 - Adamantylloxycarbonyl - D - phenylglycine.

10 6. Process for the preparation of N - adamantylloxycarbonyl derivatives of α -amino acids represented by the formula:



where

15 X is $\begin{array}{c} \text{R} \\ | \\ \text{---NH---C---} \\ | \\ \text{H} \end{array}$ or , AD is

adamantyl, methyladamantyl, dimethyladamantyl or homo-adamantyl; R is hydrogen, $\text{C}_1\text{---C}_4$ alkyl, hydroxy-substituted $\text{C}_1\text{---C}_4$ alkyl, ~~carbaloxy~~ $(\text{C}_1\text{---C}_4)$ -substituted $\text{C}_1\text{---C}_4$ alkyl, mercapto-substituted $\text{C}_1\text{---C}_4$ alkyl, $\text{C}_1\text{---C}_4$ alkylmercapto-substituted $\text{C}_1\text{---C}_4$ alkyl, guanidino-substituted $\text{C}_1\text{---C}_4$ alkyl,

phenyl, benzyl, thienyl, furyl, imidazolyl-methyl, indolylmethyl and hydroxyindolyl-methyl; R' is hydrogen or $\text{C}_1\text{---C}_4$ alkyl; R'' is hydrogen or hydroxyl; and the alkali metal and amine salts thereof, which comprises reacting an adamantyl chloroformate represented by the formula



with a compound of the formula



where AD, X and R' are defined as above in a non-acidic inert reaction medium.

7. The process of claim 6 wherein 1-adamantyl chloroformate is reacted with glycine to form N - 1 - adamantylloxycarbonyl glycine.

8. The process of claim 6 wherein 1-adamantyl chloroformate is reacted with D-phenylglycine to form N - 1 - adamantylloxycarbonyl - D - phenylglycine.

9. Process for preparing compound represented by formula (I) as defined in claim 1, substantially as herein described with particular reference to Example II or Example III.

10. The products obtained by the processes defined in any of claims 6 to 9.

BOULT, WADE & TENNANT
111 & 112, Hatton Garden, London, E.C.1.
Chartered Patent Agents
Agents for the Applicant(s)

carbaloxy

25 methyl

45

20