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4-ALLYL-1-(2-ANILINOETHYL)-4-CARBALKOXY-PIPERIDINES

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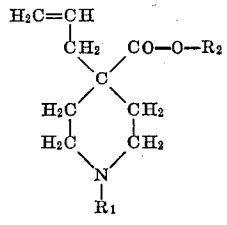
ABSTRACT OF THE DISCLOSURE

1-substituted 4-allyl-isonipecotinic acid lower alkyl esters and acid addition salts thereof which have useful analgesic and antitussive properties, therapeutical compositions containing these esters or these salts and a method of treating pain as well as a method of producing an antitussive effect, in mammals. Illustrative embodiments are 1-(3-phenylpropyl)-4-allyl-isonipecotinic acid ethyl ester and 1-n-octyl-4-allyl-isonipecotinic acid ethyl ester.

This invention relates to piperidine derivatives having valuable pharmacological properties. More particularly the invention pertains to 1-substituted 4-allyl-isonipecotinic acid lower alkyl esters and to acid addition salts thereof. The invention is further concerned with processes for the production of these compounds and these addition salts and also comprehends therapeutical compositions consisting essentially of (1) a 1-substituted 4-allyl-isonipecotinic acid lower alkyl ester according to the invention or a pharmaceutically acceptable acid addition salt thereof and (2) a pharmaceutical carrier. Furthermore, the invention pertains to a method of treating pain as well as to a method of producing an antitussive effect, in mammals.

Compounds of the formula



(I)

wherein

R_1 represents alkyl having 7 to 9 carbon atoms, phenylalkyl having at most 4 carbon atoms in the alkyl moiety, 2-(N-alkanoyl-anilino)-ethyl having at most 4 carbon atoms in the alkanoyl moiety, 2-anilinoethyl, 2-(N-allylanilino)-ethyl, 2-phenoxyethyl, 2-benzoylethyl or cinnamyl, and

R_2 represents lower alkyl,

and their addition salts with inorganic or organic acids, have not been known up to now.

The term "lower alkyl" as used herein per se means saturated monovalent aliphatic groups of the general formula $-C_mH_{2m+1}$ wherein *m* designates an integer of less than 5 and is inclusive for both straight and branched chain groups. Illustrative of such alkyl groups are e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert. butyl.

It has now been found that the inventive compounds and their acid addition salts unexpectedly exhibit valuable pharmacological properties, in particular analgesic and antitussive activity with, at the same time, a favorable therapeutical index. These pharmacological properties render the inventive compounds and their acid addition salts well suited for the treatment, relief and removal,

of pain of various origin as well as for the production of antitussive effect and the treament of tussive irritation and cough, in mammals, and thus for the use as active ingredients in the therapeutical compositions according to the invention.

The analgesic activity is particularly marked in those of the inventive compounds wherein in the above formula R_1 represents phenylalkyl having at most 4 carbon atoms in the alkyl moiety, and R_2 represents lower alkyl, especially in those compounds wherein R_1 represents phenylethyl or phenylpropyl and R_2 represents ethyl, whereas the antitussive activity, although possessed by all of the inventive compounds, is especially pronounced in those compounds of the invention wherein in the above formula R_1 represents alkyl having 7 to 9 carbon atoms, and R_2 represents lower alkyl.

The aforementioned group of compounds wherein in the above formula R_1 represents alkyl having 7 to 9 carbon atoms or phenylalkyl having at most 4 carbon atoms in the alkyl moiety, and R_2 represents lower alkyl, as well as their acid addition salts, form a preferred embodiment of the invention, together with the therapeutical compositions containing said compounds or the pharmaceutically acceptable acid addition salts thereof as active ingredients.

Particular examples among the compounds forming the preferred embodiment of the invention, which show analgesic activity to a favorable degree are: 1-(2-phenylethyl)-4-allyl-isonipecotinic acid ethyl ester, and 1-(3-phenylpropyl)-4-allyl-isonipecotinic acid ethyl ester, while examples of compounds which are distinguished by pronounced antitussive activity are particularly 1-n-octyl-4-allyl-isonipecotinic acid ethyl ester, as well as 1-(3-phenylpropyl)-4-allyl-isonipecotinic acid n - butyl ester, and 1 - (4 - phenylbutyl)-4-allyl-isonipecotinic acid ethyl ester.

The analgesic activity of the inventive compounds is determined e.g. according to the method of F. Gross, Helvet. Physiol. Acta 5, C31 (1947) with the apparatus of Friebel and may illustratively be demonstrated, for instance, for 1-(3-phenylpropyl)-4-allyl-isonipecotinic acid ethyl ester as follows:

The apparatus comprises an electrically heated lamp which is placed in the focus of a semi-elliptical metal, concave mirror. Under the mirror, on a turn-table, there are located 10 small Plexiglas cages each holding a white mouse in such a position that the mouse-tail rests stretched out in a small groove on a Plexiglas plate. The turn-table can be turned so that the mouse-tails one after the other come to be placed into the second focus of the elliptical mirror. Pain is induced by the convergent heat radiation from the mirror and the time is measured from the moment when the heat reaches the mouse-tail till the moment at which the mouse twitches its tail.

Two series of 10 mice each are tested prior to the administration of the test compound, and the normal reaction time for each mouse is recorded. Then the test compound is administered either by intraperitoneal injection or orally and the reaction times after the injection are recorded, thus enabling determination of the intensity and the duration of the analgesic effect of the test compound administered.

1-(3-phenylpropyl)-4-allyl - isonipecotinic acid ethyl ester, used in form of its fumarate, exhibits in this test during 60 minutes an average increase of 50% of the threshold of irritation (prolongation of reaction time) at doses of about 6 mg./kg. i.p. or 65 mg./kg. p.o., while having at the same time a favorable therapeutical index: the toxicity value LD_{50} of this compound in mice is >530 mg./kg. p.o.

On account of their favorable pharmacological, in particular analgesic properties, the compounds wherein in the

above formula R_1 represents phenylethyl or phenylpropyl and R_2 represents ethyl, especially 1-(3-phenylpropyl)-4-allyl-isonipecotinic acid ethyl ester as well as 1-(2-phenylethyl)-4-allylisonipecotinic acid ethyl ester, are particularly suitable for the treatment, relief or removal, of pain which comprises administering orally, rectally or parenterally to a mammal requiring such treatment an analgesically effective amount of such a compound or of a pharmaceutically acceptable acid addition salt thereof.

The antitussive activity of the inventive compounds is determined e.g. according to R. Domenjoz, Archiv für experimentelle Pathologie und Pharmakologic 215, 19–24 (1952) and may illustratively be demonstrated, for instance, for 1-(3-phenylpropyl)-4-allyl-isonipecotinic acid n-butyl ester as follows:

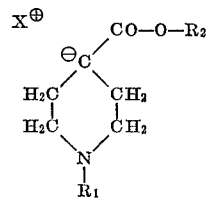
Healthy cats of normal weight are narcotized with a suitable narcotic.

Doses of 30–65 mg./kg. of aprobarbital are applied intraperitoneally to obtain a relatively superficial narcosis. About 45 minutes after the injection of the narcotic, the preparation of the Nervus laryngeus superior is started, by fitting on an irritation-electrode. An apparatus manufactured by "Grass Medical Instruments," Type SD 5, allowing irritation of the aforeside nerve with rectangular current-impulses of any desired frequency and intensity is connected to the electrode. The irritation-frequency applied is 5 cycles at an irritation-intensity between 0.5 and 3 volts. The irritation-duration is about 8 seconds and the interval between two irritations is about 120 seconds. For the registrations of the cough reflexes, a Marey capsule is used. A respiration-cannula is introduced through the oral cavity down to the glottic chink. The compound to be tested is injected intravenously in the form of a 1% aqueous solution of its fumarate.

1-(3-phenylpropyl)-4-allyl-isonipecotinic acid n-butyl ester, used in form of its fumarate, shows in this test at doses of about 0.5 mg./kg. to about 1.0 mg./kg. excellent antitussive activity.

The favorable pharmacological, especially antitussive properties of the compounds wherein R_1 represents alkyl having 7 to 9 carbon atoms and R_2 represents lower alkyl, particularly of 1-n-octyl-4-allyl-isonipecotinic acid ethyl ester, as well as of 1-(4-phenylbutyl)-4-allyl-isonipecotinic acid ethyl ester, and of 1-(3-phenylpropyl)-4-allyl-isonipecotinic acid n-butyl ester render these compounds well suited for the production of an antitussive effect as well as for the treatment of tussive irritation and cough in a mammal which comprises administering orally, rectally or parenterally to said mammal an antitussively effective amount of such a compound or of a pharmaceutically acceptable acid addition salt thereof.

The new piperidine derivatives of the Formula I and their acid addition salts can be produced starting from isonipecotinic acid alkyl esters substituted in the 1-position by the group R_1. In the process according to the invention, an alkali metal compound of an isonipecotinic acid ester corresponding to the general Formula II



(II)

wherein

$X^{\oplus}$ represents an alkali metal ion, particularly a lithium ion, and

R_1 and R_2 have the meanings given in Formula I,

is reacted in an inert organic solvent with a reactive ester of allyl alcohol and, if desired, the resulting compound of Formula I is converted into an addition salt with an inorganic or organic acid.

Halides such as the bromide, iodide and chloride, also alkane sulphonic acid esters and arene sulphonic acid esters such as methane sulphonic acid ester or p-toluene sulphonic acid ester are used in particular as reactive esters of allyl alcohol. A suitable reaction medium for the main reaction is, e.g. a mixture of anhydrous diethyl ether or tetrahhydrofuran with 1,2 - dimethoxyethane (ethylene glycol dimethyl ether). The alkali metal compounds of Formula II are produced in situ from other suitable alkali metal compounds. Triphenylmethyl lithium, which is particularly suitable as such is preferably also formed in situ from another organic lithium compound such as phenyl lithium, e.g. by adding a solution of triphenylmethane in 1,2-dimethoxyethane to phenyl lithium produced in the known way and kept in diethyl ether. As triphenylmethyl lithium produces intensively coloured solutions, both its formation and the amount used by the isonipecotinic acid ester of Formula II which is subsequently added, can easily be observed. Instead of triphenylmethyl lithium, also, e.g. triphenylmethyl sodium or potassium can be used. The steps in the process according to the invention are generally slightly exothermic and can be performed at room temperature or slightly raised temperature. Depending on the starting materials and amounts thereof used, if necessary, the reaction mixture should also be able to be cooled.

A number of 1-substituted isonipecotinic acid alkyl esters of Formula II are known and others can be produced analogously to those known in a simple manner. For example, such starting materials are obtained by quaternising lower isonipecotinic acid alkyl esters with halogen compounds of the Formula III

$$R_1\text{—Hal} \qquad \text{(III)}$$

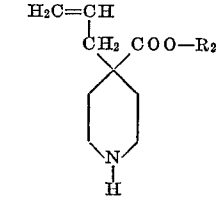
wherein

Hal represents, chlorine, bromine or iodine, and

R^1 has the meaning given in Formula I,

and then catalytically hydrogenating, e.g. in the presence of rhodium-aluminum oxide catalysts. More general is the reaction of a lower isonipecotinic acid alkyl ester with a halide of the general Formula III or with a corresponding methane sulphonic acid or p-toluene sulphonic acid ester.

Another process for producing compounds of Formula I and their salts with inorganic and organic acids consists in reacting a compound of the Formula IV



(IV)

wherein R_2 has the meaning given in Formula I, with a reactive ester of a compound of the general Formula V

$$R_1\text{—OH} \qquad \text{(V)}$$

wherein R_1 has the meaning given in Formula I. The reaction is performed at room temperature or at a moderately elevated temperature in a suitable organic solvent such as ethanol, acetone, ethyl acetate or dimethyl formamide.

If desired, the reaction is accelerated by the addition of acid binding agents such as potassium carbonate and/or potassium iodide. Suitable reactive esters are, in particular, esters of hydrogen halic acids such as bromides, chlorides and iodides, also arylsulphonic acid esters, e.g. p-toluene sulphonic acid esters.

If desired, the piperidine derivatives of Formula I obtained by a process according to the invention are then converted in the usual way into their addition salts with inorganic and organic acids. For example, the acid desired as salt component or a solution thereof is added to a solution of a piperidine derivative of Formula I

in an organic solvent such as diethyl ether, methanol or ethanol and the salt which precipitates either direct or after addition of a second organic liquid such as diethyl ether or methanol, is isolated.

Instead of the free bases, pharmaceutically acceptable acid addition salts thereof can be used as active ingredients in the therapeutical compositions according to the invention i.e. salts with those acids the anions of which, in the usual dosages, have either none or a desirable pharmacological action in themselves. In addition, it is of advantage if the salts to be used as active ingredients crystallise well and are not or are only slightly hygroscopic. Hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methane sulfonic acid, ethane sulfonic acid, β-hydroxyethane sulfonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid, embonic acid or 1,5-naphthalenedisulfonic acid, for example, can be used for salt formation with piperidine derivatives of Formula I.

As mentioned above the piperidine derivatives of Formula I and their salts are administered to mammals orally, rectally or parenterally.

The daily dosages of the free bases or of pharmaceutically acceptable salts thereof will, of course, vary with the mammal under treatment and may, for example, range between about 1 mg. and about 100 mg. Suitable dosage units of the therapeutical compositions according to the invention such as dragées (sugar coated tablets), capsules, tablets, suppositories or ampoules, preferably contain 0.5–50 mg. of piperidine derivative of the Formula I or a pharmaceutically acceptable acid addition salt thereof.

Also lozenges and forms not made up in oral single dosages are used in particular for the treatment of coughs, e.g. cough syrups and drops prepared with the usual auxiliaries.

Dosage units for oral administration preferably contain between 1% and 90% of a piperidine derivative of the Formula I or a pharmaceutically acceptable acid addition salt thereof as active substance. They are produced by combining the active substances with, e.g. solid pulverulent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols of suitable molecular weights, to form tablets or dragée cores. The latter are coated, e.g. with concentrated sugar solutions which can contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a laquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to distinguish between different dosages of active substance. Other suitable dosage units for oral administration are hard gelatine capsules as well as soft, closed capsules made of gelatine and a softener such as glycerine. The former contain the active substance preferably as granulate in admixture with lubricants such as talcum or magnesium stearate and, optionally, stabilising agents such as sodium metabisulphite or ascorbic acid. In soft capsules the active substance is preferably dissolved or suspended in suitable liquids such as liquid polyethylene glycols, to which stabilising agents can also be added.

Examples of dosage units for rectal administration are suppositories which consist of a combination of a piperidine derivative of Formula I or a suitable salt thereof with a neutral fatty foundation, or also gelatine rectal capsules which contain a combination of the active substance with polyethylene glycols of suitable molecular weight.

Ampoules for parenteral, particularly intramuscular, also intravenous, administration preferably contain a water soluble salt of a piperidine derivative of the general Formula I as active substance in a concentration of, preferably, 0.5–5%, in aqueous solution, optionally together with suitable stabilising agents and buffer substances.

The following prescriptions further illustrate the production of tablets, dragées, syrups and drops:

(a) 10.0 g. of active substance, e.g. 1-(3-phenylpropyl)-4-allyl isonipecotinic acid ethyl ester fumarate, 30.0 g. of lactose, and 5.0 g. of highly dispersed silicic acid are mixed, the mixture is moistened with a solution of 5.0 g. of gelatine and 7.5 g. of glycerine in distilled water and granulated through a sieve. The granulate is dried, sieved and carefully mixed with 3.5 g. of potato starch, 3.5 g. of talcum and 0.5 g. of magnesium stearate. The mixture is pressed into 1,000 tablets each weighing 65 mg. and containing 10 mg. of active substance.

(b) 5.0 g. of active substance, e.g. 1-(2-phenylethyl)-4-allyl isonipecotinic acid ethyl ester fumarate, 15.0 g. of lactose and 20.0 g. of starch are mixed, the mixture is moistened with a solution of 5.0 g. of gelatine and 7.5 g. of glycerine in distilled water and granulated through a sieve. The granulate is dried, sieved and carefully mixed with 3.5 g. of talcum and 0.5 g. of magnesium stearate. The mixture is pressed into 1,000 dragée cores. These are then coated with a concentrated syrup made from 26.660 g. of crystallised saccharose, 17.500 g. of talcum,, 1.000 g. of shellac, 3.750 g. of gum arabic, 1.000 g. of highly-dispersed silicic acid and 0.090 g. of dyestuff and dried. The dragées obtained each weigh 110 mg. and contain 5 mg. of active substance.

(c) 20 g. of 1-(3-phenylproply)-4-allyl-isonipecotinic acid n-butyl ester fumarate, 42 g. of p-hydroxybenzoic acid methyl ester, 18 g. of p-hydroxybenzoic acid propyl ester and 5,000 g. of crystallized sugar and also any flavoring desired are dissolved in distilled water up to 10 liters to give a cough-syrup.

(d) To produce drops for the treatment of coughs, 500 g. of 1-n-octyl-4-allyl-isonipecotinic acid ethyl ester fumarate, 10 g. of ascorbic acid, sweetener, e.g. 5. g. of sodium cyclamate, flavoring as desired and 2,500 g. of sorbitol (70%) are dissolved in distilled water up to 10 liters.

The following non-limitative examples further illustrate the invention. The temperatures are given in degrees centigrade, percentages are given by weight.

EXAMPLE 1

11.0 g. of bromobenzene in 100 ml. of abs. ether are placed in a 350 ml. four-necked flask and 0.93 g. of lithium wire cut into small pieces and washed with petroleum ether are added while stirring under an atmosphere of nitrogen whereupon the ether begins to boil. After the reaction has subsided, the mixture is refluxed for another 2½ hours. 17.1 g. of triphenylmethane in 80 ml. of abs. 1,2-dimethoxyethane are poured all at once into the solution of phenyl lithium obtained whereupon, due to the formation of the triphenylmethyl lithium, the solution turns deep red coloured and gently boils. After stirring for 20 minutes at room temperature, 18.3 g. of 1-(3-phenylpropyl)-isonipecotinic acid ethyl ester in 20 ml. of abs. ether are added at 28°. The temperature of the solution slightly rises and it loses its deep red colour. It is stirred for 10 minutes at room temperature and then 8.45 g. of allyl bromide in 20 ml. of abs. ether are added all at once. The mixture is stirred for 2½ hours at room temperature whereupon it turns yellow and lithium bromide precipitates. 10 ml. of water are then added to the reaction mixture and it is evaporated in a rotary evaporator. Ether is added to the residue and the ether solution obtained is extracted with dilute hydrochloric acid. The acid extracts are made alkaline and extracted exhaustively with chloroform and the chloroform extracts are dried and concentrated. The residue is taken up in ether, the ether solution is dried and concentrated and the residue is distilled. The 1-(3-phenylpropyl)-4-allyl isonipecotinic acid ethyl ester boils at 178°/0.01 torr. The oil is dissolved in ether and 95% of the theoretical amount of

fumaric acid is added. The fumarate is filtered off under suction and recrystallised from isopropanol. The 1-(3-phenylpropyl)-4-allyl isonipecotinic acid ethyl ester fumarate melts at 138°.

The following compounds are produced analogously:

1-n-heptyl-4-allyl-isonipecotinic acid ethyl ester;
1-n-octyl-4-allyl-isonipecotinic acid ethyl ester, B.P. 130–140°/0.01 torr, fumarate M.P. 147–148°;
1-n-nonyl-4-allyl-isonipecotinic acid ethyl ester;
1-benzyl-4-allyl-isonipecotinic acid ethyl ester, B.P. 135–143°/0.4 torr, hydrochloride M.P. 148°;
1-(2-phenylethyl)-4-allyl-isonipecotinic acid ethyl ester, B.P. 125–130°/0.01 torr, fumarate M.P. 138°;
1-(2-phenoxyethyl)-4-allyl-isonipecotinic acid ethyl ester, B.P. 186–193°/1.0 torr, fumarate M.P. 107–108°;
1-(3-phenylpropyl)-4-allyl-isonipecotinic acid methyl ester, B.P. 130–150°/0.01 torr, fumarate M.P. 181–182°;
1-(3-phenylpropyl)-4-allyl-isonipecotinic acid propyl ester, B.P. 145–150°/0.01 torr, fumarate M.P. 138–139°;
1-(3-phenylpropyl)-4-allyl-isonipecotinic acid butyl ester, B.P. 172–182°/0.09 torr, fumarate M.P. 146–147°;
1-(3-phenylpropyl)-4-allyl-isonipecotinic acid isopropyl ester, B.P. 140–150°/0.01 torr, hydrochloride M.P. 163–165°;
1-(2-phenylpropyl)-4-allyl-isonipecotinic acid ethyl ester, B.P. 124–136°/0.03 torr, fumarate M.P. 114–116°;
1 - [2 - (N-propionyl-anilino)-ethyl]-4-allyl-isonipecotinic acid ethyl ester;
1 - [2-(N-allyl-anilino)-ethyl]-4-allyl-isonipecotinic acid ethyl ester;
1 - cinnamyl-4-allyl-isonipecotinic acid ethyl ester, B.P. 143–152°/0.01 torr, fumarate M.P. 133–134°;
1-(4-phenylbutyl)-4-allyl-isonipecotinic acid ethyl ester, B.P. 136–147°/0.01 torr, fumarate M.P. 101–102°.

The 1-substituted isonipecotinic acid alkyl ester needed as starting materials for the production of the above compounds can be produced, e.g., as follows:

(a) 20 g. of isonipecotinic acid ethyl ester and 75.5 g. of 3-phenylpropyl bromide in 100 ml. of ethanol are refluxed for 5 hours. The ethanol is then evaporated off in vacuo, the residue is dissolved in water and the aqueous solution is extracted three times with ether. On evaporating the aqueous solution in vacuo and finally under high vacuum, the ethyl ester of 4-carboxy-1-(3-phenylpropyl-pyridinium bromide remains.

(b) 24.1 g. of the above quaternary salt in 200 ml. of ethanol are hydrogenated at room temperature under 3–4 atm. pressure in the presence of rhodium-aluminium oxide catalyst (5% Rh). The catalyst is then filtered off and the filtrate is evaporated. The residue is covered with chloroform and made alkaline with concentrated sodium hydroxide solution. The chloroform is removed and the aqueous phase is exhaustively extracted with chloroform. The combined chloroform solutions are washed with saturated sodium chloride solution, dried and concentrated and the residue is distilled under high vacuum. The 1-(3-phenylpropyl)-isonipecotinic acid ethyl ester boils at 130–143°/0.08 torr.

EXAMPLE 2

1.1 g. of 4-allyl-isonipecotinic acid ethyl ester, 2.2 g. of 2-phenylethyl bromide, 5 g. of sodium carbonate and 0.1 g. of sodium iodide in 40 ml. of acetone are refluxed for 18 hours. The reaction mixture is then filtered, the filter residue is washed with acetone, the filtrate is concentrated and the residue is distilled under high vacuum. The 1 - (2-phenylethyl)-4-allyl-isonipecotinic acid ethyl ester boils at 125–130°/0.01 torr. The fumarate produced therefrom melts at 138°.

The following are produced analogously:

1 - [2 - (N-propionyl-anilino)-ethyl]-4-allyl-isonipecotinic acid ethyl ester;
1-(2-anilionethyl)-4-allyl-isonipecotinic acid ethyl ester;
1-(2-benzoylethyl)-4-allyl-isonipecotinic acid ethyl ester;
1-(3-phenylpropyl)-4-allyl-isonipecotinic acid ethyl ester, B.P. 178°/0.01 torr, fumarate M.P. 138°;
1-n-octyl-4-allyl-isonipecotinic acid ethyl ester, B.P. 130–140°/0.01 torr, fumarate M.P. 147–148°;

and all other compounds listed in Example 1.

4-allyl-isonipecotinic acid ethyl ester needed as starting material is produced as follows:

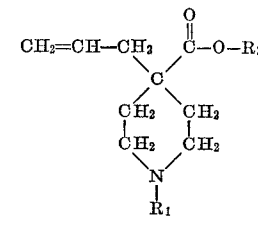
(a) 2.03 g. of lithium wire cut out into small pieces are added to 22.8 g. of bromobenzene in 180 ml. of anhydrous ether in a 750 ml. four-necked flask, the addition being made under an atmosphere of nitrogen. The ether begins to boil. After the reaction has diminished, the mixture is refluxed for another 2½ hours. 35.4 g. of triphenylmethane in 150 ml. of abs. 1,2-dimethoxyethane are added all at once to the solution of phenyl lithium obtained whereupon, due to the formation of triphenylmethyl lithium, the solution turns deep red and gently boils. After stirring for 20 minutes at room temperature, 42.3 g. of 1-benzyloxycarbonyl-isonipecotinic acid ethyl ester in 50 ml. of anhydrous ether are added at 28°. (This ethyl ester is produced by reacting isonipecotinic acid ethyl ester with chloroformic acid benzyl ester in the presence of 1 N sodium bicarbonate solution.) The solution loses its deep red color and the temperature slightly rises. It is stirred for 10 minutes at room temperature and then 18.0 g. of allyl bromide in 40 ml. of anhydrous ether are added all at once. The mixture is stirred at room temperature for 2½ hours whereupon it turns yellowish and lithium bromide precipitates. 40 ml. of water are then added to the reaction mixture which is then evaporated almost to dryness in a rotary evaporator. The residue is taken up in 50 ml. of ether and the ether solution obtained is extracted three times with 2 N hydrochloric acid. The ether solution is dried and concentrated and the residue is left to stand overnight whereupon the triphenylmethane crystallises out. The whole mixture is then suspended in cold methanol, the triphenylmethane is filtered off under suction and the residue is distilled under high vacuum. The 1-benzyloxycarbonyl-4-allyl-isonipecotinic acid ethyl ester passes over at 170–192°/0.07 torr.

(b) 8.0 g. of 1-benzyloxycarbonyl-4-allyl-isonipecotinic acid ethyl ester are stirred in a 100 ml. round flask by means of a magnetic stirrer with 40 ml. of a saturated solution of hydrobromic acid in glacial acetic acid and 9 ml. of anhydrous ether. The initial strong development of carbon dioxide gradually diminishes. The reaction solution is then evaporated in a rotary evaporator and the residue is taken up in 6 N hydrochloric acid. The hydrochloric acid solution is extracted with ether, then made alkaline with concentrated ammonia while cooling and extracted with chloroform. The chloroform solution is dried, concentrated and the 4-allyl-isonipecotinic acid ethyl ester which remains is immediately further reacted.

The other low alkyl esters of 4-allyl-isonipecotinic acid can also be produced analogously to (a) and (b).

What is claimed is:

1. A compound of the formula:



wherein

R_1 is 2-anilinoethyl of 2-(N-allylanilino)ethyl; and

R_2 is lower alkyl.

2. A compound according to claim **1** wherein R_1 is [2-(N-allylanilino)-ethyl] and R_2 is ethyl.

3. A pharmaceutically acceptable acid addition salt of a compound as defined in claim 2.

4. A compound, according to claim 1 wherein R_1 is 2-anilinoethyl and R_2 is ethyl.

5. A pharmaceutically acceptable acid addition salt of a compound according to claim 4.

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