United States Patent Office 3,108,113 Patented Oct. 22, 1963

3,108,113

GAMMA-AMINOBUTYRYL NICOTINATE

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No Drawing. Filed Oct. 24, 1960, Ser. No. 64,282
6 Claims. (Cl. 260—295.5)

This invention is concerned with gamma-aminobutyryl nicotinate and its method of preparation. This new chemical compound is useful in the therapy of neurogenic vasospasm.

It has been known that the reduction of blood flow through an organ may result from excessive central nervous system activity. Such reduced blood flow may be caused by a narrowing of the blood vessels, especially the arteries, arterioles and capillaries, because of an increase in muscle tonus. The diminished blood flow may give rise to distressing symptoms of pain and discomfort as well as result in more severe pathologic states which involve thromboembolism from blood stasis and eventually gangrene.

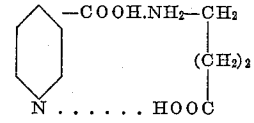
These pathologic states have been treated in the past with vasodilating agents which are capable of causing an increased blood flow. However, this class of compounds has many inherent limitations which restricts their use. Thus, for example, those agents which are derived from (or related to) epinephrine have a special effect upon the heart such serious side-reactions sometimes resulting in death. Other members of this class of drugs, which act by blocking the transmission of the nerve impulse as, for example, ganglionic blocking agents, affect the blood pressure as well and give rise to a state of hypotension which in turn may lead to fainting and weakness.

While the untoward effects of the conventional vasodilating drugs are by no means limited to the described symptoms, the common appearance of side-reactions which require special care and dosage regulation during therapy, result in denial of the drugs to a large group of patients suffering from neurogenic vasospasm. Furthermore, the conventional vasodilating drugs have a limited order of activity which is essentially restricted to the larger trunk vessels and have little or no effect on the causative mechanism arising in the brain cell. In contrast to this, the product of the present invention is capable of causing an increased blood-flow by counteracting excessive neuronal transmission and, at the same time, causing vasodilation without superimposing the noxious effects of the common vasodilating drugs. Gamma-aminobutyryl nicotinate depresses neuronal transmission, thereby relaxing spastic contraction. At the same time it acts to dilate the smaller arterioles and capillary bed, thereby improving circulation through a muscle area.

The special therapeutic advantages of gamma-aminobutyryl nicotinate may be demonstrated by its effect in the relief of the symptoms of primary dysmenorrhea. Primary dysmenorrhea occurs without evident organic cause. The symptoms usually present themselves in ovulatory cycles, often ending with the first pregnancy. Although primary dysmenorrhea is generally considered to be functional, nevertheless, evidence of nerve pathology has been demonstrated, and the association between the symptoms of the disease and the psychologic well-

being of the patient have been interrelated. While there has been considerable uncertainty and confusion concerning the etiology and pathogenesis of primary dysmenorrhea, its symptoms and therapeutic approaches have been studied in great detail. Analgesics and anti-spasmodics appear to be of only moderate value. The use of hormones has been cautiously employed because of the dangers from adverse reactions arising from a disturbance of the endocrine balance. This condition, which has been related to a neurogenic vasospastic origin, is presently treated with a wide variety of drugs, with little therapeutic success. However, the distressing symptoms of primary dysmenorrhea may be successfully combatted by the administration of gamma-aminobutyryl nicotinate in spite of the fact that it has no analgesic or sedative properties.

Gamma-aminobutyryl nicotinate is prepared through the reaction between gamma-aminobutyric acid and nicotinic acid in anhydrous alcoholic media. Equimolar amounts of the reacting compounds are dissolved in an anhydrous alcohol as, for example, absolute isopropyl alcohol, and the mixture refluxed for four hours. The alcohol is then concentrated until a slurry forms, and the whole set aside to crystallize in an ice chest. The crystals of gamma-aminobutyryl nicotinate are then filtered and dried. The structural formula is:



An alternate method of preparation of gamma-aminobutyryl nicotinate is to neutralize the solution of gamma-aminobutyric acid in 0.1 N hydrochloric acid with a metallic salt of nicotinic acid as, for example, sodium, calcium, potassium, copper, magnesium or silver in the presence of freshly precipitated silver hydroxide or copper powder. The yield of a compound by either of these methods is excellent, and the resulting product may be used in therapy without further purification.

The compound is stable and may be formulated into pharmaceutical preparations which are both efficacious and safe for therapeutic purposes. The administration of gamma-aminobutyryl nicotinate to humans does not cause the undesirable side reactions which have been reported for the group of compounds known as vasodilators; nor does it appear to act through the same pharmacologic mechanisms as do the principal members of this therapeutic group.

Gamma-aminobutyryl nicotinate provides a dual attack upon the problem of neurogenic vasospasm by exerting a neuronal, depressant effect upon synaptic transmission, at the same time that a local stimulatory action occurs at the end-organ site. Thus, by depressing the level of excessive stimulae originating in the central nervous system (which tend to cause the local vasoconstrictions) at the same time that the dilatory mechanism of the blood vessels is stimulated, an effective synergistic therapeutic action results. This synergism of the therapeutic activity of the component moieties, which is superior to the mere additive enhancement of the specific and independent pharmacologic actions of the component fractions, may be demonstrated by the reduced dosage

equivalence of the therapeutic agent required to produce the increased effect. This synergistic attack upon the neurogenic vasospasm, furthermore, is not limited to any specific disease entity, but rather to the broader pathologic states in which this condition is found, whether as a symptom or etiologic factor.

When it is desired to use gamma-aminobutyryl nicotinate for therapeutic purposes, it may be prescribed in the form of a tablet or capsule for oral administration or as a hydro-alcoholic solution. Regardless of the dosage form utilized, the average dosage range of the active compound is from 20 mg. to 2 gm. per day, depending upon the particular patient's needs, administered in divided doses—each containing 200 mg. of the active compound. Individual dosage forms whether solid or liquid consist of from 5 to 300 mg. of gamma-aminobutyryl nicotinate in a compatible pharmaceutical diluent or carrier. In the case of solid forms such carrier may be lactose, starch, sucrose, monnitol, or any of the other compatible carriers. In the case of the liquid form, the carrier may be ethanol, sorbitol, propylene glycol, glycerine or any other compatible carrier.

The following examples illustrate our invention:

Example I

In a suitable round-bottom glass boiling flask, fitted with a dropping funnel, reflux condenser and stirrer, is placed one liter of a solution of one-tenth mol of gamma-aminobutyric acid dissolved in absolute isopropyl alcohol. Hydrogen chloride gas is passed through the solution until one reacting-equivalent of hydrogen chloride has been absorbed by the solution. The flow of gas is then stopped and a solution of 1.3 mols of sodium nicotinate dissolved in one liter of isopropanol is then added to the acidified solution of gamma-aminobutyric acid, followed by one-half gram of finely divided copper powder. The mixture is stirred at room temperature for approximately twenty minutes and then the temperature is gradually elevated to refluxing. The mixture is refluxed for one hour and then cooled to room temperature.

There is an immediate separation of sodium chloride which is filtered from the solvent and the clear filtrate concentrated to one-tenth its original volume and then set aside to crystallize in an ice chest. The crystals are filtered, washed with two portions of cold isopropyl alcohol and then dried. The dried white crystals of gamma-aminobutyryl nicotinate melt at 147–148° C., and analyze for carbon, hydrogen and nitrogen in good agreement with the theoretical values.

Theory.—Carbon 53.33; hydrogen 5.77; nitrogen 12.44.

Found.—Carbon 53.16; hydrogen 6.47; nitrogen 12.60.

It is soluble in organic polar solvents such as, alcohol, acetone and chloroform. It is insoluble in water, petroleum ether and benzene. The molecular weight of the compound is 225.23.

Example II

To a solution of 1 mol of gamma-aminobutyric acid, dissolved in two liters of methanol, is added 1.1 mols of nicotinic acid and the mixture refluxed for four hours. The solvent is then distilled and the residue crystallized from isopropyl alcohol, using a ratio of five parts of alcohol for every part of dried residue. The resulting crystals are gamma-aminobutyryl nicotinate melting at 147–148° C., and conform in every respect to those obtained as a result of Example I above.

Example III

In place of the dry hydrogen chloride used in Example I, may be substituted an equimolar amount of hydrochloric acid, or hydrogen bromide gas, or hydrobromic acid, or sulphuric acid, or nitric acid; although from the viewpoint of ease of synthetic procedure, hydrogen chloride is the preferred reagent. When any of the other inorganic acids are used, the reaction will proceed exactly as described above, with the other steps remaining the same. Should it be desired to utilize an organic acid, for example, acetic, propionic, butyric, citric, or tartaric acid, in place of the hydrogen chloride as described in Example I, then the procedure must be modified in order to separate the formed sodium acid salt from the mother liquor. This is accomplished through the use of fractional crystallization techniques which are well known to the organic chemist. An example of such a technique is to add an equal volume of acetone to the concentrated alcohol solution of gamma-aminobutyryl nicotinate. On standing, a flocculent precipitate of the sodium acid salt forms which is filtered and the filtrate concentrated to one-half the volume and then set aside to crystallize. The remaining steps are carried out as described in Example I. It is recognized that the use of an organic acid, as a means of facilitating the synthesis of gamma-aminobutyryl nicotinate, will appreciably increase the cost of the final product. In addition the yield of the final compound might not be comparable to those obtained after the use of the inorganic acids.

Example IV

In place of the isopropyl alcohol used as a solvent in Example I, and the methanol used as the solvent in Example II, there may be substituted any liquid alcohol of a class ROH, wherein R is either a straight or branched chain alkyl group from 1 to 6 carbon atoms in length. The other steps are carried out exactly as described in Examples I and II.

Example V

In place of the copper powder used as a catalyst in Example I, there may be substituted freshly precipitated silver hydroxide. When copper powder or silver hydroxide is used as a catalyst for this reaction, the amounts which are to be used are from 0.1 to 0.5 gram of either copper powder or silver hydroxide for each 0.5 mol of gamma-aminobutyric acid obtained (calculated).

Example VI

When it is desired to utilize gamma-aminobutyryl nicotinate in therapy it may be administered in the form of a tablet or capsule or hydro alcoholic solution. The dosage range employed is from 20 mg. to 2 gm. per day administered in divided doses dependent upon the individual patient's needs. For optimal flexibility in dosage administration it is preferred that each unit dose contain 200 mg. although greater or lesser amounts may be employed as indicated above, and as the condition of a particular user dictates.

Because of the stability of gamma-aminobutyryl nicotinate no special techniques are necessary for the compounding of pharmaceutically useful tablets and capsules.

For the preparation of a liquid solution, so that each teaspoonful contains 200 mg. gamma-aminobutyryl nicotinate, the vehicle used is 20 to 30 percent ethanol and the active ingredient is dissolved in the solvent to form a solution which may then be flavored to taste.

What is claimed is:

1. Gamma-aminobutyryl nicotinate.

2. The method of preparing gamma-aminobutyryl nicotinate which comprises the steps of intermixing gamma-aminobutyric acid and nicotinic acid in an inert organic solvent and recovering from the reaction mixture gamma-aminobutyryl nicotinic acid.

3. The method of preparing gamma-aminobutyryl nicotinate which comprises the steps of intermixing an acid salt of gamma-aminobutyric acid and a metallic salt of nicotinic acid in the presence of an inert solvent and recovering from the resulting reaction mixture gamma-aminobutyryl nicotinate.

4. The method of claim 3, there being added to the reaction mixture a compound selected from the group consisting of freshly precipitated silver hydroxide and copper powder.

5. The method of preparing gamma-aminobutyryl nicotinate which comprises the steps of intermixing equimolar quantities of gamma-aminobutyric acid and a metallic salt of nicotinic acid in a liquid medium selected from the group consisting of alkyl alcohols which contain 1–6 carbon atoms and recovering from the reaction mixture gamma-aminobutyryl nicotinate.

6. The method of preparing gamma-aminobutyryl nicotinate which comprises the steps of intermixing a salt selected from the group consisting of the hydrochloride, hydrobromide, sulphate and nitrate acid salts of gamma-aminobutyric acid and a metallic salt of nicotinic acid in an alcoholic medium and recovering from the resulting reaction mixture gamma-aminobutyryl nicotinate.

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