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3-PYRIDINE CARBINOL NITRATE AND ITS PREPARATION

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This invention is concerned with a new and novel heterocyclic nitrate ester and its water-soluble, pharmaceutically acceptable salts, the method for their preparation and their use as pharmaceutical compounds. In particular, it is concerned with the nitrate ester of 3-pyridine carbinol and its water-soluble, pharmaceutically acceptable salts which are useful in the treatment of coronary artery disease and to produce peripheral blood vessel dilation.

The organic nitrates are used in therapy to lower the tonus of the arterial wall, thereby relieving arterial spasm. The vasodilatation resulting after the administration of organic nitrates can be demonstrated directly by plethysmographic measurements and by the onset of a blushing phenomenon due to a dilation of the superficial vessels of the body. While the degree of vasodilation varies with both the quantity of available nitrate radicals of the particular molecule as well as the organic nucleus, the nitrate compounds have a common site of action which has been established to be directly upon the contractile substance of the blood vessels. It is generally assumed that the organic nitrates act only after being reduced to nitrites; but since excised vessels react promptly to nitrates, they may perhaps act directly as well. It should be noted in this connection, that the effective dose of glyceryl trinitrate is one-hundredth that of sodium nitrate and on the basis of available nitrite ion, the fatal dose of sodium nitrite for rabbits after intravenous injection is at least twice that of glyceryl trinitrate. Thus, it might be postulated that the organic nitrates act independently although through a similar mechanism as do nitrites or that the reduction of the nitrate group occurs at the site of action.

The most important effect of this class of compounds is the action on the coronary vessels and the peripheral circulation resulting in an increased blood flow. The use of the nitrates in relieving the pain of coronary vasospasm and angina pectoris has been known for almost 100 years. Similarly, the effect of the nitrates in causing vasodilation of the peripheral arteries has also been firmly established in therapy.

Despite the long term awareness of the beneficial properties of this class of compounds and their widespread usage in therapy, there are many inherent limitations in the use of this class of compounds with the result that of the literally hundreds of thousands of organic nitrate compounds known to chemical literature, only a few have been introduced therapeutically and many of these have been subsequently discarded.

The principal limitation inherent to this class of compounds is their unpredictable duration of action, the onset of noxious side reactions and the development of a tolerance requiring increasing dosages to maintain the therapeutic effect. Thus, some of the nitrates act within seconds while others require an hour before an effect is observed. The duration of action may vary from a few minutes to more than four hours for a given dosage. These wide differences seriously limit the therapeutic application of the individual drugs in that the emergency nature of the attack of coronary artery disease does not permit a latent period of an unpredictable nature. Similarly, the marked variation in the duration of action is also a limiting factor.

The seriousness of utilizing a vasodilating compound which has a pronounced effect in dilating the peripheral vessels, without a cooncomitant effect on the coronary circulation, is readily apparent when we consider the danger of depriving the heart itself of an adequate supply of blood because large amounts of blood are shunted from visceral to peripheral vessels. This shunting of blood from the cardiac to the peripheral circulation represents a serious potential hazard to the patient with coronary insufficiency.

In general, nitrate esters may be divided into two therapeutic classifications which are based upon their duration of activity. The first group are rapid-acting series and consist of compounds which are easily absorbed, as for example, glyceryl trinitrate, amyl nitrite and sodium nitrite. These agents are of value in providing prompt relief from the exruciating pain of the acute attack of angina pectoris. However, these agents generally exert their effect for such short periods of time that they are of little or no value in the prevention of the anginal attack. The second group consists of the relatively insoluble nitrate esters which are not readily absorbed from the gastrointestinal tract. These agents have a long latent period for the onset of their therapeutic effect. Their slower absorption accounts for their more prolonged duration of action. Such drugs as mannitol hexanitrate, erythritol tetranitrate and pentaerythritol tetranitrate are examples of this class of nitrate esters.

A fundamental limitation of the nitrate group as a whole is their tendency to produce a dilation of the meningeal vessels, resulting in headaches. These headaches, which last for an indeterminate period of time, may be so distressing to the patient that the administration of the drug may have to be halted. The headache produced by these compounds is primarily due to meningeal congestion which has been confirmed by direct microscopic observation. The brain volume was also observed to increase in man, as did the pressure of the cerebrospinal fluid.

Gastrointestinal distress has also been observed as a side reaction to the administration of nitrates primarily as a result of the hydrolysis of the esters with consequent liberation of nitric acid and also as a result of the direct action of the nitrate ester on the gastrointestinal tract.

Vaying degrees of nervousness and anxiety have been observed in some patients after the administration of nitrates, as well as edema, excessive sweating and visual disturbances.

A tolerance to the action of a therapeutic dose of the nitrates develops on the continued administration of virtually all of the older preparations. This tolerance requires either that the drug be withdrawn for a period of time or that increasingly larger doses be utilized. Since many of the conventional nitrates are utilized at the near toxic level, further increase in the dosage is not feasible, and, consequently, the patient is denied the therapeutic benefit of the drug.

Thus, it has been a goal of therapeutic research to develop a nitrate compound which would be rapidly absorbed, preferably by either the sublingual or the oral route and would have a minimal period of onset of action as well as possessing a sustained therapeutic effect. Such a drug might be used to provide a prompt relief of the acute anginal episode and for prophylactic therapy as well.

In contrast to the properties of the older members of this class of compounds, the nitrate ester of 3-pyridine carbinol and its water-soluble, pharmaceutically acceptable salts are readily absorbed by either the sublingual or oral routes of administration and exert their effect promptly after administration, which is sustained over a pro-

longed period of time. The compounds, when used in therapeutic dosages, are significantly free of toxic side reactions and cause a prompt increase in arterial blood flow.

In the preparation of the 3-pyridine carbinol nitrate ester it is preferred to first form a salt of 3-pyridine carbinol, for example the nitrate, and then proceed with the formation of the nitrate ester. The advantage of this procedure is the following: since the formation of the ester takes place in the presence of concentrated nitric, which is a strong oxidizing agent, there is great danger of ovidizing the alcohol group of the 3-pyridyl carbinol to an aldehyde or an acid. This undesirable reaction which can proceed concurrently with the ester formation or might, if proper precautions are not taken, even completely supersede it, obviously can greatly affect the yield and the purity of the desired ester. In order to obviate it, it is necessary to keep the temperature below 20° and preferably in the range of 0–5°. The reaction of salt formation between 3-pyridine carbinol and nitric acid, or any other strong acid, is a highly exothermic reaction which tends to keep the temperature up if the 3-pyridine carbinol base is added directly to the nitrating mixture containing concentrated nitric acid and would, furthermore, tend to dilute the nitric acid, which is undesirable. By forming the salt first, as a separate step, and then subjecting it to the ester formation this strongly exothermic phase is eliminated and the formation of the ester can proceed readily and in good yield. However, it must be noted, that while this procedure offers the advantage of great convenience, the two steps, i.e. the salt formation and the esterification may be combined. In this case, however, strong agitation and cooling must be used.

While any of the halogen acid salts may be utilized, the nitrate salt is preferred and this salt of 3-pyridine carbinol is easily formed by the direct interaction of nitric acid and the pyridine compound, in water. This resultant salt is nitrated to form the ester through the use of concentrated nitric acid in acetic anhydride. While acetic anhydride is a preferred adjunct to the nitration process, aliphatic acid anhydrides such as propionic acid anhydride and butyric acid anhydride may be used also. This may be purified to chemical purity thru the use of paired solvent crystallization procedures.

The nitrate salt of the nitrate ester of 3-pyridine carbinol may also be obtained from the reaction between a 3-halomethylpyridine hydrohalide and silver nitrate in an inert solvent, such as an alkanol containing from one to five carbon atoms or water. The nitrate salt of the nitrate ester of 3-pyridine carbinol stays in solution after the insoluble silver halide is removed by filtration. When this procedure is followed, two mols of silver nitrate per mol of hydrohalide salt are used, and water is the preferred solvent. The nitrate salt of the nitrate ester of 3-pyridine carbinol is obtained and isolated from the aqueous solution by fractional precipitation.

The nitrate salt of the nitrate ester of 3-pyridine carbinol, is a white crystalline compound with a melting point of 112° C. to 114° C. It is freely soluble in water, resulting in a clear, colorless solution with an acid reaction. The compound analyzes for elemental nitrogen in good agreement with the theoretical values, as for example, theory: percent nitrogen, 19.3; found: percent nitrogen, 19.0.

The nitrate salt of the nitrate ester of 3-pyridine carbinol has an LD_{50} of 650 mg./kg. when administered intravenously to mice and 800 mg./kg. when administered orally to mice. The ratio between the intravenous LD_{50} and the oral LD_{50} indicates that the compound is virtually completely absorbed when administered by mouth. The ability of the compound to traverse the gastrointestinal system so that it is readily absorbed and thereby causes an elevated blood level, permits a more predictable effect as well as a more prompt therapeutic action.

Dilute aqueous solution applied to the skin of the forearm of man rapidly causes the development of an intense erythema without any evidence of irritation. This demonstrates that the compound is rapidly absorbed through intact skin and causes a direct dilation of the blood vessels. When a solution of the nitrate ester of 3-pyridine carbinol is used to perfuse an isolated heat-lung preparation in the dog, utilizing a heart-lung machine and a complete by-pass system, it causes pronounced coronary vasodilation, the blood flow data with respect to a series taken, being shown in Table I.

TABLE I.—THE EFFECT OF THE NITRATE SALT OF 3-PYRIDINE CARBINOL NITRATE ON CORONARY BLOOD FLOW IN THE DOG

Body Temperature, °F.	Control Blood Flow (without drugs) cc./min.	The Nitrate Salt of 3-Pyridine Carbinol Nitrate	
		Total Dose, mg.	Coronary Blood Flow, cc./min.
93.9	112	10	122
Dog #1[a] 90.9	83	20	105
89.7–89.8	72	20	88
Dog #2[b] 93.9	61	10	74
90.9	63	20	52
98	100	40	160
			180
Dog #3[c] 94	60	40	105
80	50	40	80
			75

[a] Weight, 16 kg.; Weight of Heart (wet basis), 110 gm.; Constant extracorporeal blood flow from Sigma motor pump required to maintain dog's blood pressure at start and throughout experiment, 800 cc./min.
[b] Weight, 16 kg.; Weight of Heart (wet basis), 110 gm.; Constant extracorporeal blood flow from Sigma motor pump required to maintain blood pressure at start and throughout experiment, 425 cc./min.
[c] Weight, 16 kg.; Weight of Heart (wet basis), 110 gm.; Constant extracorporeal blood flow from Sigma motor pump required to maintain blood pressure at start and throughout experiment, 425 cc./min.

When this compound is administered intravenously to an anesthetized dog at a dosage level of 10.0 mgm./kg., the mean blood pressure drops (within 10 seconds) from 140 mm. Hg, to 63 mm. Hg. At the end of 90 minutes the mean blood pressure is 118 mm. Hg, although the cardiac rate does not then return to the pretreatment level. The blood pressure and the cardiac rate return to the pretreatment level approximately two hours after the administration of the compound. Evidence of vasodilatation is seen in the increased corneal vascularization which followed the administration of the compound and persisted during the period of pharmacologic response.

In the conscious dog, the duration of activity is approximately 75 minutes and the blood pressure decreases from 185 mm. Hg to 93 mm. Hg, and stabilizes at an average of 125 mm. Hg. In contrast to this, nitroglycerin produces a drop in blood pressure of approximately 30 mm. Hg for a duration of only 4 to 5 minutes.

The administration of the compound by the sublingual route to an anesthetized dog results in a marked vasodilator activity and the parameters of the pharmacologic effect as evidenced by the changes in mean blood pressure, pulse pressure and cardiac rate, observed for more than 90 minutes, were identical in character to those observed after intravenous administration, and were observed to persist for more than 90 minutes.

The following examples illustrate the scope of the present invention.

Example 1

To a mixture of 10 ml. of 67 to 69 perecnt (concentration by weight) nitric acid and 10 ml. of water, is slowly added, with stirring, 5.45 gm. of 3-pyridine carbinol. The resulting solution is evaporated to drynes under vacuum (below 15 mm. Hg) on a waterbath. The residue is stirred with ether to crystallize and the crystals are filtered, washed in ether and dried under vacuum. These crystals consist of the nitrate salt of 3-pyridine carbinol, which melts at 106° to 107° C. The nitrate salt of 3-pyridine carbinol may be further purified, if desired, by

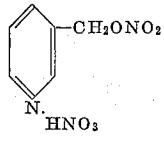
dissolving in boiling isopropanol. Upon cooling, it crystallizes.

12.4 ml. of 90 percent (concentration by weight) nitric acid was added slowly with stirring to 41 ml. of acetic anhydride at 5° to 10° C. To this mixture was added, at about 0° to 5° C., 10 gm. of the nitrate salt of 3-pyridine carbinol (obtained above). The resulting solution of reagents is maintained at a temperature of not more than 20° C. and, preferably, from 0° to 5° C. for approximately three hours and then an equal volume of benzene is added which is followed by an excess of hexane. Alternately, aromatic solvents such as benzene, toluene, xylene, alkyl naphthalene and alkyl benzene (wherein the alkyl moiety has from 1 to 6 carbon atoms) may be employed, and in lieu of hexane, there may be used such aliphatic solvents as pentane, heptane, octane and nonane.

The mixture forms two layers. The upper layer is separated and discarded, while the remaining lower layer is again treated with benzene and hexane as described above. After the separation of the layers, the lower layer is again separated and mixed with an equal volume of benzene and the whole brought into homogeneous solution by the addition of isopropanol. The solution is cooled in an ice chest and allowed to crystallize. The separated crystals are filtered, washed with benzene and dried.

The resulting compound is the nitrate salt of the nitrate ester of 3-pyridine carbinol or the nitrate salt of 3-pyridine carbinol nitrate and is a white crystalline compound, melting at 112° to 114° C. The crystals are freely soluble in water to provide a clear, colorless solution with an acid reaction. When tested for nitrogen content by the micro-Dumas method, it was found to contain 19.0 percent of nitrogen, which is in good agreement with the theoretical calculated value of 19.3 percent nitrogen. A mixed melting point of the nitrate salt of 3-pyridine carbinol and the nitrate salt of the nitrate ester of 3-pyridine carbinol establishes that the two chemicals are different compounds, since the melting point of the mixture of these substances is 80° to 85° C. Furthermore, the addition of ammonia to an aqueous solution of the nitrate salt of the nitrate ester of 3-pyridine carbinol causes the separation of a water insoluble oil which is the nitrate ester of 3-pyridine carbinol. In contrast to this, the nitrate salt of 3-pyridine carbinol does not yield a water insoluble oil upon treatment with ammonia water.

The structure of the nitrate salt of 3-pyridine carbinol nitrate is:



Example 2

To produce a 3-pyridine carbinol nitrate, alkali is added (as for example, potassium hydroxide) to aqueous solutions of the nitrate salt of the nitrate ester of 3-pyridine carbinol nitrate. The oil is extracted with an inert, immiscible, volatile solvent such as ether, benzene, chlorofor, hexane, benzin, toluene, alkyl benzene, xylene, alkyl naphthalene, heptane and octane (wherein alkyl refers to alkyl moieties having from 1 to 6 carbon atoms), the solvent evaporated and the isolated oil recovered. After the proof of structure, this may be further hydrolyzed by alkali to 3-pyridine carbinol. A determination of the neutralization equivalent, arrived at in this manner, indicates that 21.8 mg. of the nitrate salt of the nitrate ester of 3-pyridine carbinol is equivalent to 1 ml. of 0.5 N KOH. The theoretical quantity of this ester salt, equivalent to 1 ml. of 0.5 N KOH, is calculated to be 21.6 mg.

Example 3

A solution of 0.652 gm. (0.004 mol) of 3-chloromethylpyridine hydrochloride in 5 ml. ethanol is added dropwise to a solution of 1.353 gm. (0.008 mol) of silver nitrate in 20 ml. ethanol and 3 ml. water. The silver nitrate solution is warmed on the steam bath during the addition. After the solution is completed the reaction mixture is heated for one more hour on the steam bath to digest the precipitate of silver chloride. The precipitate is removed by filtration, and on standing at room temperature, the filtrate yields an additional precipitate of silver chloride which is removed by filtration. The filtrate is evaporated to dryness and the residue recrystallized from isopropanol. The product melted at 112° to 114° C.

Example 4

In place of the 3-chloromethylpyridine hydrochloride used in Example 1, there may be substituted, in equimolar amounts, 3-bromomethyl-pyridine hydrobromide and 3-iodomethylpyridine hydroiodide, and the remainder of the steps being the same. The product isolated is the nitrate salt of the nitrate ester of 3-pyridine carbinol, identical in every respect to that obtained as the result of the steps of Example 1.

Example 5

In place of the ethanol used in Example 1 above, there may be substituted any member of the group of alkanols of from 1 through 6 carbons, water or mixtures of these and the remainder of the steps being the same.

Example 6

When it is desired to utilize, therapeutically, the nitrate salt of the nitrate ester of 3-pyridine carbinol nitrate, it may be administered in the form of tablets or capsules. The range in concentration of the active substance (the nitrate salt of 3-pyridine carbinol nitrate) is from 1 mg. to 200 mg., administered from one to six times daily, depending upon the status of hte patient and the degree of disease present.

To prepare tablets of the nitrate salt of the nitrate ester of 3-pyridine carbinol, the appropriate quantity of the compound is mixed with a diluent or carrier, such as milk sugar, sucrose, corn starch, potato starch or mannitol. The ratio of active compound to diluent ranges from equal parts of active compound and diluent to one part active compound and 99 parts of diluent. The exact proportions to be used in any particular formation depends upon the concentration of active substance desired in the final formulation. To the mixture of the active substance-diluent is then added 0.05 part of a lubricant such as magnesium stearate or vegetable fats (a brand of which is known to the trade as "Sterex") and the whole wetted with a solution of 5 percent gelatin-water or 0.05 percent tragacanth-water or 20 percent alcohol-water, and the damp mass passed through a No. 16 mesh screen and dried. To the dried material is then added an equal part of corn starch and 0.05 parts of the same lubricant and the whole passed through a No. 40 to a No. 60 mesh screen and then tableted in the selected size and shape.

While the unit dosage range of the active ingredient per tablet is from 1 to 200 mg., a preferred range will be found to be between 5 and 100 mg. per tablet, administered one to six times daily.

It may be desired to administer this compound in a capsule dosage form in which case the mixture of the active ingredient, diluent and lubricant is granulated with a solution of 5 percent gelatin-water or 0.05 percent tragacanth-water or 20 percent alcohol-water, and the damp mass passed through a No. 40 to a No. 60 mesh screen and dried. The dried material may be filled directly into capsules of suitable size so that each capsule contains between 1 to 200 mg. of the nitrate salt of the nitrate ester of 3-pyridine carbinol, and a preferred range will be found to be between 25 and 100 mg. per capsule, which is to be administered one to six times daily.

Example 7

When it is desired to cause a vasodilation of the arteries and arterioles, as well as in the capillary bed, the nitrate salt of the nitrate ester of 3-pyridine carbinol is administered in unit dosage form as a tablet or capsule, each containing from 1 to 200 mg. of the nitrate salt of 3-pyridine carbinol nitrate, per tablet or capsule. A promp vasodilating effect will be observed and an increase in both segmental and digital blood flow may be ascertained by either plethysmographic or oscillometric instruments. Vasodilatation of the coronary vessels is also manifested by an increased blood flow which is evidenced through the relief of the symptoms of the coronary vasospasm.

In order to maintain a prolonged or extended therapeutic effect, the tablets or capsules may be administered at a frequency of from one to six times daily, depending upon the patient's needs. This daily administration may be repeated for as long as is necessary.

Example 8

When it is desired to relieve the symptoms of coronary vasospasm and to augment the reduced peripheral blood flow of the extremities, as would be present in Buerger's disease, or Raynaud's Phenomenon, intermittent claudication and peripheral vasospasm, then tablets or capsules of the nitrate salt of the nitrate ester of 3-pyridine carbinol, each containing from 1 to 200 mg. of the said compound, may be administered, from one to six times daily, depending upon the patient's needs. In the treatment of such diseases with this compound, the drug may be administered for as long as is necessary.

It is not desired to be limited except as set forth in the following claims, the above description being by way of illustration of the invention.

What is claimed is:

1. A compound selected from the group consisting of the nitrate ester of 3-pyridine carbinol and its water-soluble pharmaceutically acceptable salts.

2. Nitrate ester of 3-pyridine carbinol.

3. The nitrate salt of the nitrate ester of 3-pyridine carbinol.

4. A method of preparing the nitrate salt of the nitrate ester of 3-pyridine carbinol which comprises reacting a hydrohalide salt of a 3-halomethylpyridine with silver nitrate in an inert liquid medium.

5. A method according to claim **4**, wherein the hydrohalide salt of a 3-halomethyl-pyridine is selected from the group consisting of 3-chloromethylpyridine hydrochloride, 3-bromomethylpyridine hydrobromide, and 3-iodomethylpyridine hydroiodide.

6. A method of preparing the nitrate salt of the nitrate ester of 3-pyridine carbinol which comprises treating 3-chloromethylpyridine hydrochloride with two equivalents of silver nitrate in aqueous solution.

7. A method of preparing the nitrate ester of 3-pyridine carbinol which comprises treating an aqueous solution of the nitrate salt of the nitrate ester of 3-pyridine carbinol with alkali.

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