United States Patent [19]

Stehle et al.

[11] **3,829,579**

[45] **Aug. 13, 1974**

[54] **STABLE SOLUTIONS OF PGE-TYPE COMPOUNDS**

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[22] Filed: **May 11, 1973**

[21] Appl. No.: **359,486**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 194,686, Nov. 1, 1971, abandoned.

[52] **U.S. Cl.**..... **424/312,** 424/318, 260/468 D, 260/514

[51] **Int. Cl.**..... **A61k 27/00**

[58] **Field of Search**..... 424/318, 312

[56] **References Cited**

OTHER PUBLICATIONS

Brummer – J. Pharmacy & Pharmacology, Vol. 23, (1971), pages 804 & 805.

Primary Examiner—Sam Rosen

[57] **ABSTRACT**

Stable solutions of PGE-type compounds are obtained by dissolving the compounds in an anhydrous, water-miscible, pharmacologically acceptable, dipolar aprotic solvent.

16 Claims, No Drawings

STABLE SOLUTIONS OF PGE-TYPE COMPOUNDS

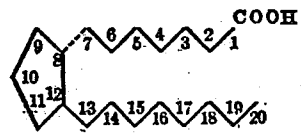
CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of our copending application Ser. No. 194,686, filed Nov. 1, 1971, now abandoned.

DESCRIPTION OF THE INVENTION

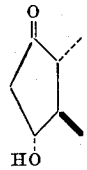
This invention relates to novel compositions of matter and to methods for using same. More specifically, this invention is concerned with novel solutions of prostaglandin-like compounds of the PGE-type in an anhydrous, water-miscible, pharmacologically acceptable, dipolar aprotic solvent in a concentration of at least one mg. per ml. This invention also relates to a process for dispensing prostaglandin-like compounds of the PGE-type which comprises dissolving the compound in an anhydrous, water-miscible, pharmacologically acceptable, dipolar aprotic solvent in a concentration of at least one mg. per ml.; packaging the resulting solution in unit dose containers; diluting the contents of a container into a liquid or solid vehicle; and administering said vehicle to administer a therapeutic dose. This invention also relates to a process for dispensing prostaglandin-like compounds of the PGE-type which comprises dissolving said compound in an anhydrous, water-miscible, pharmacologically-acceptable, dipolar aprotic solvent in a concentration of at least 1 mg. per ml. sterilizing the resulting solution; aseptically packaging it in sterile containers in unit doses; diluting the contents of a sterile container with a sterile miscible diluent and administering the solution at a rate to administer a therapeutic dose.

Prostaglandins are related in structure to the substance known as prostanoic acid which has the following structural formula and atom numbering:



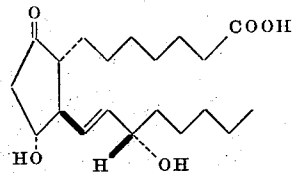
I

Prostaglandins of the E-type (PGE-type) all have the following structural feature:



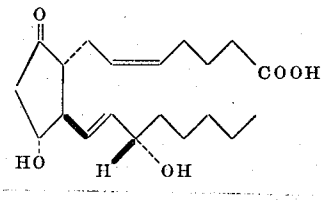
II

The prostaglandin known as prostaglandin E_1 (PGE_1) has the formula:



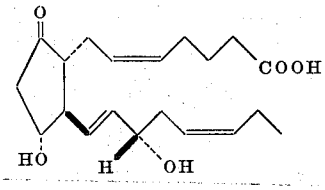
III

The prostaglandin known as prostaglandin E_2 (PGE_2) has the formula:



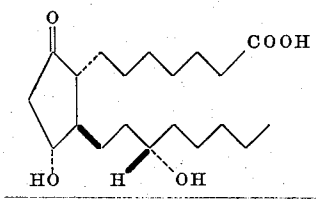
IV

The prostaglandin known as prostaglandin E_3 (PGE_3) has the formula:



V

The prostaglandin known as dihydroprostaglandin E_1 (dihydro-PGE_1) has the formula:



VI

Esters of prostaglandins of the E-type are also known in the art. See, for example, U.S. Pat. Nos. 3,069,322 and No. 3,598,858.

As is known in the art, prostaglandins of the E-type and their esters are extremely potent in causing various biological responses. For that reason, these compounds are useful for pharmacological and pharmaceutical purposes. See, for example, Bergstrom et al., Pharmacol. Rev. 20, 1 (1968), and references cited therein. A few of those biological responses are systemic blood pressure lowering as measured, for example, in anesthetized (pentobarbital sodium) pentolinium-treated rats with indwelling aortic and right heart cannulas; stimulation of smooth muscle as shown, for example, by tests on strips of guinea pig ileum, rabbit duodenum, or gerbil colon; potentiation of other smooth muscle stimulants; antilipolytic activity as shown by antagonism of epinephrine-induced mobilization of free fatty acids or inhibition of the spontaneous release of glycerol from isolated rat fat pads; inhibition of gastric secretion as shown in dogs with secretion stimulated by food or histamine infusion; activity on the central nervous system; controlling spasm and facilitating breathing in asthmatic conditions; and decreasing blood platelet adhesiveness as shown by platelet-to-glass adhesiveness, and inhibition of blood platelet aggregation and thrombus formation induced by various physical stimuli, e.g., arterial injury, and various biochemical stimuli, e.g., ADP, ATP, serotonin, thrombin, and collagen.

Because of these biological responses, these known prostaglandins of the E-type and their esters are useful to study, prevent, contrOl, or alleviate a wide variety of diseases and undesirable physiological conditions in birds and mammals, including humans, useful domestic animals, pets, and zoological specimens, and in laboratory animals, for example, mice, rats, rabbits, and monkeys.

For example, these E-type prostaglandins are useful in mammals, including man, as nasal decongestants. For this purpose, the compounds are used in a dose range of about 10 μg. to about 10 mg. per ml. of a phar-

macologically suitable liquid vehicle or as an aerosol spray, both for topical application.

The E-type prostaglandins are useful in the treatment of asthma. For example, these compounds are useful as bronchodilators or as inhibitors of mediators, such as SRS-A, and histamine which are released from cells activated by an antigen-antibody complex. Thus, these compounds control spasm and facilitate breathing in conditions such as bronchial asthma, bronchitis, bronchiectasis, pneumonia and emphysema. For these purposes, these compounds are administered in a variety of dosage forms, e.g., orally in the form of tablets, capsules, or liquids; rectally in the form of suppositories; parenterally, subcutaneously, or intramuscularly, with intravenous administration being preferred in emergency situations; by inhalation in the form of aerosols or solutions for nebulizers; or by insufflation in the form of powder. Doses in the range of about 0.01 to 5 mg. per kg. of body weight are used 1 to 4 times a day, the exact dose depending on the age, weight, and condition of the patient and on the frequency and route of administration. For the above use these prostaglandins can be combined advantageously with other anti-asthmatic agents, such as sympathomimetics (isoproterenol, phenylephrine, ephedrine, etc.); xanthine derivatives (theophylline and aminophylline); and corticosteroids (ACTH and predinisolone). Regarding use of these compounds see South African Pat. No. 681,055.

The E-type prostaglandins are useful in mammals, including man and certain useful animals, e.g., dogs and pigs, to reduce and control excessive gastric secretion, thereby reducing or avoiding gastrointestinal ulcer formation, and accelerating the healing of such ulcers already present in the gastrointestinal tract. For this purpose, the compounds are injected or infused intravenously, subcutaneously, or intramuscularly in an infusion dose range about 0.1 μg. to about 500 μg. per kg. of body weight per minute, or in a total daily dose by injection or infusion in the range about 0.1 to about 20 mg. per kg. of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

The E-type prostaglandins are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, and to remove or prevent the formation of thrombi in mammals, including man, rabbits, and rats. For example, these compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent post-operative thrombosis, to promote patency of vascular grafts following surgery, and to treat conditions such as atherosclerosis, arteriosclerosis, blood clotting defects due to lipemia, and other clinical conditions in which the underlying etiology is associated with lipid imbalance or hyperlipidemia. For these purposes, these compounds are administered systemically, e.g., intravenously, subcutaneously, intramuscularly, and in the form of sterile implants for prolonged action. For rapid response, especially in emergency situations, the intravenous route of administration is preferred. Doses in the range about 0.005 to about 20 mg. per kg. of body weight per day are used, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

The E-type prostaglandins are especially useful as additives to blood, blood products, blood substitutes, and other fluids which are used in artificial extracorporeal circulation and perfusion of isolated body portions, e.g., limbs and organs, whether attached to the original body, detached and being preserved or prepared for transplant, or attached to a new body. During these circulations and perfusions, aggregated platelets tend to block the blood vessels and portions of the circulation apparatus. This blocking is avoided by the presence of these compounds. For this purpose, the compound is added gradually or in single or multiple portions to the circulating blood, to the blood of the donor animal, to the perfused body portion, attached or detached, to the recipient, or to two or all of those at a total steady state dose of about 0.001 to 10 mg. per liter of circulating fluid. It is especially useful to use these compounds in laboratory animals, e.g., cats, dogs, rabbits, monkeys, and rats, for these purposes in order to develop new methods and techniques for organ and limb transplants.

The E-type prostaglandins are extremely potent in causing stimulation of smooth muscle, and are also highly active in potentiating other known smooth muscle stimulators, for example, oxytocic agents, e.g., oxytocin, and the various ergot alkaloids including derivatives and analogs thereof. Therefore, PGE_2, for example, is useful in place of or in combination with less than usual amounts of these known smooth muscle stimulators, for example, to relieve the symptoms of paralytic ileus, or to control or prevent atonic uterine bleeding after abortion or delivery, to aid in expulsion of the placenta, and during the puerperium. For the latter purpose, the E-type prostaglandin is administered by intravenous infusion immediately after abortion or delivery at a dose in the range about 0.01 to about 50 μg. per kg. of body weight per minute until the desired effect is obtained. Subsequent doses are given by intravenous, subcutaneous, or intramuscular injection or infusion during puerperium in the range 0.01 to 2 mg. per kg. of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal.

The E-type prostaglandins are useful as hypotensive agents to reduce blood pressure in mammals, including man. For this purpose, the compounds are administered by intravenous infusion at the rate about 0.01 to about 50 μg. per kg. of body weight per minute or in single or multiple doses of about 25 to 500 μg. per kg. of body weight total per day.

The E-type prostaglandins are useful in place of oxytocin to induce labor in pregnant female animals, including man, cows, sheep, and pigs, at or near term, or in pregnant animals with intrauterine death of the fetus from about 20 weeks to term. For this purpose, the compound is infused intravenously at a dose of 0.01 to 50 μg. per kg. of body weight per minute until or near the termination of the second stage of labor, i.e., expulsion of the fetus. These compounds are especially useful when the female is one or more weeks post-mature and natural labor has not started, or 12 to 60 hours after the membranes have ruptured and natural labor has not yet started. An alternative route of administration is oral.

The E-type prostaglandins are useful for controlling the reproductive cycle in ovulating female mammals, including humans and animals such as monkeys, rats,

rabbits, dogs, cattle, and the like. By the term ovulating female mammals is meant animals which are mature enough to ovulate but not so old that regular ovulation has ceased. For that purpose, PGE_2, for example, is administered systemically at a dose level in the range 0.001 mg. to about 2 mg. per kg. of body weight of the female mammal, advantageously during a span of time starting approximately at the time of ovulation and ending approximately at the time of menses or just prior to menses. Intravaginal and intrauterine are alternative routes of administration. Additionally, expulsion of an embryo or a fetus is accomplished by similar administration of the compound during the first third of the normal mammalian gestation period.

The E-type prostaglandins are useful in causing cervical dilation in pregnant and nonpregnant female mammals for purposes of gynecology and obstretrics. In labor induction and in clinical abortion produced by these compounds, cervical dilation is also observed. In cases of infertility, cervical dilation produced by PGE and PGF compounds is useful in assisting sperm movement to the uterus. Cervical dilation by prostaglandins is also useful in operative gynecology such as D and C (Cervical Dilation and Uterine Curettage) where mechanical dilation may cause perforation of the uterus, cervical tears, or infections. It is also useful in diagnostic procedures where dilation is necessary for tissue examination. For these purposes, the PGE-type compounds are administered locally or systemically. PGE_2, for example, is administered orally or vaginally at doses of about 5 to 50 mg. per treatment of an adult female human, with from one to five treatments per 24 hour period. PGE_2 is also administered intramuscularly or subcutaneously at doses of about one to 25 mg. per treatment. The exact dosages for these purposes depend on the age, weight, and condition of the patient or animal.

As mentioned above, the E-type prostaglandins are potent antagonists of epinephrine-induced mobilization of free fatty acids. For this reason, this compound is useful in experimental medicine for both in vitro and in vivo studies in mammals, including man, rabbits, and rats, intended to lead to the understanding, prevention, symptom alleviation, and cure of diseases involving abnormal lipid mobilization and high free fatty acid levels, e.g., diabetes mellitus, vascular diseases, and hyperthyroidism.

Many prostaglandin-like compounds of the PGE-type are also known in the art. All of these have the same cyclopentane ring structural feature of formula II, above, but differ from the prostaglandins of the E-type in one or more other structural aspects, for example, in having one or more substituents, for example, alkyl, fluoro, phenyl, or cycloalkyl, on either or both side chains, in having fewer or more methylene groups in one or both of the side chains, in having a hetero atom, for example, oxygen in place of a side-chain methylene group, in having cis rather than a trans or a trans rather than a cis configuration for a side-chain carbon-carbon double bond, or in any combination of those structural aspects. With reference to the numbering system of prostanoic acid (formula I above), some examples of E-type prostaglandin-like compounds are 15-methyl-PGE_1, 15β-15-methyl-PGE_1, 15-methyl-PGE_2, 15β-15-methyl-PGE_2, 16,16-dimethyl-PGE_1, 16,16-dimethyl-PGE_2, 3-oxa-PGE_1, 3-oxa-PGE_2, 7-oxa-PGE_1, 17-phenyl-18,19,20 -trinor-PGE_2, PGE_1 15-methyl ether, PGE_2 15-methyl ether, 5,6-trans-PGE_2, 20-ethyl-PGE_2, 20-methyl-PGE_1, 16-fluoro-PGE_2, and the esters of all of those. As examples of prior art which disclose these E-type prostaglandin-like compounds and others of the E-type, see German Offenlegungschrift Nos. 1,937,675, 1,937,921, 2,011,969, 2,036,471, 2,118,686, 2,121,980, 2,144,048, 2,150,361, 2,154,309, 2,165,184, 2,209,990, 2,217,044, and 2,221,443. See also French Pat. No. 2,119,855, Dutch Pat. application No. 7,206,316, and Belgian Pat. Nos. 779,898 and 782,822, these being available in printed form through Derwent CPI accession Nos. 76213T-B, 76383T-B, 59033T-B, and 72340T-B, respectively.

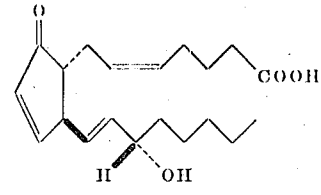
The above-described structural variants of the E-type prostaglandins are useful for the same purposes described above for the E-type prostaglandins, and are used for those purposes in the ways described above.

For the purposes of this invention, the term "prostaglandin-like compounds of the E-type" includes both prostaglandins of the E-type, namely PGE_1, PGE_2, PGE_3, dihydro-PGE_1, and the esters of those, and also other carboxylic and esters thereof of the type exemplified above, namely those which are structurally similar to the E-type prostaglandins, having a cyclopentane moiety of formula II but with structural variations in either or both side chains, and causing at least part of the biological responses caused by E-type prostaglandins.

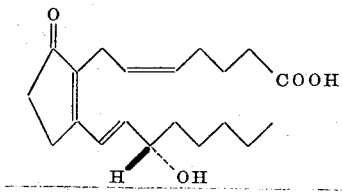
Also for the purposes of this invention, the term "prostaglandin-like compounds of the E-type" is intended to include optically active compounds with the same absolute configuration as optically active PGE_1 obtained from certain mammalian tissues, for example, sheep vesicular glands or human seminal plasma. See, for example, Bergström et al., J. Biol. Chem. 238, 3555 (1963). This term is also intended to include racemic compounds but not the enantiomers of said optically active compounds. Thus, for example, the compound designated PGE_2 means an optically active compound with the natural configuration, and the corresponding racemate, and the compound designated 15-methyl-PGE_2 means an optically active compound with the absolute configuration of PGE_1, and also the corresponding racemate.

Also for the purposes of this invention, the term "prostaglandin-like compounds of the E-type" is intended to include not only the carboxylic acids but also the esters of said carboxylic acids. Typical esters are those wherein the esterifying radical is alkyl of one to 12 carbon atoms, inclusive, cycloalkyl of three to 10 carbon atoms, inclusive, aralkyl of seven to 12 carbon atoms, inclusive, phenyl, and phenyl substituted with one, 2, or 3 chloro or alkyl of one to four carbon atoms, inclusive. Especially useful for the above described purposes are alkyl esters of one to four carbon atoms, inclusive, more especially methyl and ethyl esters.

One problem that has been observed in using and formulating prostaglandin-like compounds of the E-type is the stability of the compounds. These compounds tend to decompose, especially at room temperatures, e.g., about 25° C., and higher, and especially in the presence of small amounts of acid or base. In particular, in the presence of acid, PGE_2, for example, changes to PGA_2 which has the formula:



In the presence of base, PGE_2 changes to PGB_2 which has the formula:



Similarly, the other prostaglandin-like compounds of the E-type change to the corresponding compounds of the A-type or the B-type. Even in neutral solution or in the solid state, there is a gradual change of E-types to A-types and B-types.

Reasonable stability of prostaglandin-like compounds of the E-type has been observed in some solutions or in solid form when those are maintained at very low temperatures, for example, at −20° C. or lower. However, storage under such temperature conditions is usually inconvenient when the compounds are being used for the above-described purposes.

We have now discovered that solutions of prostaglandin-like compounds of the PGE-type, for example, PGE_2, in an anhydrous, water-miscible, pharmacologically-acceptable, dipolar aprotic solvent are surprisingly and unexpectedly stable even at room temperature, e.g., about 25° C., and above. Stock solutions of the E-type prostaglandin-like compound so prepared, i.e., in an anhydrous, water-miscible, pharmacologically-acceptable, dipolar aprotic solvent, for example, anhydrous N,N-dimethylacetamide, can be stored at such temperatures for relatively long periods of time, for example, up to a year or more depending on the particular solvent and its water content, without excessive decomposition. Such solutions, therefore, provide a satisfactory method for storing the prostaglandin-like E-type compounds. Such solutions also provide a satisfactory method for dispensing the prostaglandin-like E-type compounds. For example, such a solution is packaged in unit dose containers, and when used, the contents of a container are diluted into a liquid or solid carrier for administration of a therapeutic dose. For example, the solution is diluted into water for enteral administration or into lactose tablets or a suppository base for intravaginal or rectal administration. When parenteral administration of the prostaglandin-like E-type compound is intended, such solutions are dispensed by sterilizing the solution, for example, by filter sterilization, and then aseptically packaging the solution in sterile containers in unit doses, diluting the contents of a sterile container with a sterile miscible diluent, for example, water, or isotonic saline or glucose solution, and then administering the diluted solution at a rate to administer a therapeutic dose.

While anhydrous N,N-dimethylacetamide is given by way of illustration, it is to be understood that other pharmacologically acceptable, dipolar aprotic solvents can be used. Other suitable dipolar aprotic solvents include tetramethylurea, hexamethylphosphoramide, dimethylsulfoxide, sulfolane, acetone and isopropyl methyl ketone. The dipolar aprotic solvents, especially N,N-dimethylacetamide, have great solvent power for prostaglandin-like E-type prostaglandins, and, moreover, give very stable solutions.

By water-miscible is intended those solvents which mix with water in all proportions or which are so highly soluble in water that they behave as if they were completely miscible.

It is desirable that the solutions according to the invention be relatively concentrated, i.e., concentrated relative to the effective concentration, i.e., the concentration at which the drug is used. Thus with N,N-dimethylacetamide or dimethylsulfoxide, or like dipolar aprotic solvent, the concentration could be as high as 100 mg./ml. or so. Ordinarily it will be sufficient if the solute is present in at least about 1 mg. per ml. Such solutions, though seemingly dilute, are relatively quite concentrated with respect to the effective concentration.

It is to be understood that pharmacologically acceptable is to be based on the liquid or solid vehicle rather than on the stock solution. Some anhydrous solvents, for example, might not be pharmacologically acceptable undiluted as in the stock solution but are very much so when diluted with a large volume of water as in enteral or parenteral administration or when diluted into a lactose tablet or suppository base for intravaginal or rectal administration. For example, 1 ml. of a 50 mg./ml. solution of PGE_2, for example, diluted into 1 liter of infusion solution gives a solution containing 0.005 percent PGE_2. At the same time the concentration of the solvent, 0.1 percent, is well below that safe for intravenous infusion. Thus a pharmacologically acceptable solvent as used herein is one which on dilution into the liquid or solid vehicle causes no untoward pharmacodynamic effect.

An anhydrous solution is to be considered as one containing not more than 0.5 percent of water. All commercially available solvents contain water. Ordinary "pure" N,N-dimethylacetamide, for example, may contain up to about 0.5 percent water whereas "spectrograde" N,N-dimethylacetamide may contain as little as 0.03 percent water. An anhydrous solvent, therefore, is to be considered as one containing not more than about 0.5 percent water. The Karl Fischer method can be used to determine the water content. It is actually preferred that the solvent, for example, N,N-dimethylacetamide, contain not more than about 0.1 percent water.

The invention can now be more fully understood by reference to the following examples in which the parts and percentages are by weight and the units in the C.G.S. system unless otherwise specified. Although all of these examples relate to PGE_2 and N,N-dimethylacetamide, it is to be understood that other prostaglandin-like E-type compounds in both free acid form and ester form within the above-defined scope of this invention, including the compounds specifically named hereinabove, are transformed into stable solutions adapted for dispensing as set forth hereinabove, and that other anhydrous, water-miscible, pharmacologically acceptable, dipolar aprotic solvents than N,N-dimethylacetamide are also used for that purpose.

EXAMPLE 1

Parenteral grade PGE_2 is dissolved in anhydrous N,N-dimethylacetamide containing 0.4 percent water (determined by the Karl Fischer method) in the proportions of 5 mg. PGE_2 for each ml. of anhydrous N,N-dimethylacetamide. The solution is then filter sterilized by passing it through a microporous (solvent-resistant)

filter, e.g., Millipore Solvinert 0.25 microns or Gelman Metricel Alpha-8, 0.2 microns, aseptically packaged in 1 ml. quantities in sterile ampuls and kept under refrigeration at not more than 5° until needed. At that time the contents of one ampul (1 ml.) are diluted into 1 l. of infusion solution and administered intravenously at the rate of 5 mcg. of PGE_2 per minute. This regimen is intended for therapeutic abortion.

EXAMPLE 2

Parenteral grade PGE_2 is dissolved in spectrograde N,N-dimethylacetamide (0.1 percent water) in a concentration of 10 mg. per ml. The solution is filter sterilized as in Example 1 and packaged aseptically in 0.5 ml. quantities in sterile ampuls. This solution can be stored at room temperature. It is administered in the same way and for the same purposes as in Example 1.

EXAMPLE 3

Parenteral grade PGE_2 is dissolved in anhydrous N,N-dimethylacetamide (0.1 percent water) in the proportions of 0.75 mg. PGE_2 to 1.5 ml. anhydrous N,N-dimethylacetamide. The solution is then filter sterilized as in Example 1, aseptically packaged in 1.5 ml. quantities in sterile ampuls, and kept under refrigeration at not more than 5° until needed. It is administered by diluting the contents of 1 ampul (1.5 ml.) into 150 ml. of infusion solution and administered intravenously at the rate of 0.5 mcg. of PGE_2 per minute. This regimen is intended for inducing labor.

We claim:

1. A solution of a prostaglandin-like compound of the PGE-type in an anhydrous, water-miscible, pharmacologically acceptable, dipolar aprotic solvent in a concentration of at least 1 mg. per ml.

2. A solution according to claim **1** which is sterile.

3. A solution of a prostaglandin-like compound of the PGE-type in anhydrous N,N-dimethylacetamide in a concentration of at least 1 mg. per ml.

4. A solution according to claim **3** which is sterile.

5. A solution according to claim **3** wherein said compound is PGE_1 or PGE_1 methyl ester.

6. A solution according to claim **3** wherein said compound is 15-methyl-PGE_1 or 15-methyl-PGE_1 methyl ester.

7. A solution according to claim **3** wherein said compound is 15-methyl-PGE_2 or 15-methyl-PGE_2 methyl ester.

8. A solution according to claim **3** wherein said compound is 15β-15-methyl-PGE_1 or 15β-15-methyl-PGE_1 methyl ester.

9. A solution according to claim **3** wherein said compound is 15β-15-methyl-PGE_2 or 15β-15-methyl-PGE_2 methyl ester.

10. A solution according to claim **3** wherein said compound is 16,16-dimethyl-PGE_1 or 16,16-dimethyl-PGE_1 methyl ester.

11. A solution according to claim **3** wherein said compound is 16,16-dimethyl-PGE_2 or 16,16-dimethyl-PGE_2 methyl ester.

12. A solution according to claim **3** wherein said compound is 17-phenyl-18,19,20-trinor-PGE_2 or 17-phenyl-18,19,20-trinor-PGE_2 methyl ester.

13. A solution of PGE_2 in an anhydrous, water-miscible, pharmacologically acceptable, dipolar aprotic solvent in a concentration of at least 1 mg. per ml.

14. A solution according to claim **13** in which the solvent is anhydrous N,N-dimethylacetamide.

15. A solution according to claim **14** in which said N,N-dimethylacetamide contains not more than 0.1 percent water.

16. A solution according to claim **15** which is sterile.

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