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ANALGESIC COMPOSITION CONSISTING OF
MORPHINES AND AMINO-INDANES

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This invention relates to analgesic compositions consisting essentially of an analgesic compound of the morphine type, including synthetic analogs, and a 2-amino-indane compound, together with an inert carrier.

Morphine and analogs of this compound are used as strong analgesics. However, due to their respiratory and mood depression effects, the administration of such valuable analgesics must, in some cases, either be minimized or completely withheld. This is not altogether desirable since morphine and various compounds related to it are, at times, the only drugs which can effectively produce analgesia. Another factor to be considered is that of addiction. When drugs such as morphine are administered to a chronically ill patient, it is desirable to maintain a state of analgesia over an extended period of time. Under these circumstances, it is quite common for the patient to develop tolerance to the drug, requiring greater and greater doses with the passage of time, and withdrawal of the drug after prolonged treatment is usually accompanied by severe mental and physical disorders.

During recent years many attempts have been made to find synthetic drugs which possess all of the desirable attributes of morphine and similar drugs without their attendant toxic effects. Some effort has also been made to synthesize compounds which are structurally related to morphine and show the analgesic effects of the alkaloid, but are devoid of the toxic properties of the latter. However, the degree of success achieved has been minimal.

I have now found that a combination consisting essentially of (a) an analgesic of the morphine type, (b) a 2-amino-indane compound, and (c) an inert carrier represents an excellent and strong analgesic preparation.

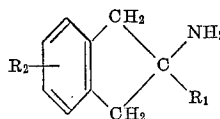
The 2-amino-indane compounds of the composition have analgesic properties of their own. However, they also exert a potentiating effect upon the analgesic effect of the morphine-type analgesic. Such potentiation of analgesia is completely unpredictable; the net effect of the potentiation by the 2-amino-indane compound of the compounds of the morphine series is that the former can be administered safely in small doses, thus minimizing the toxic side reactions while at the same time imparting the desired analgetic effect. Furthermore, the 2-amino-indane compounds, in addition to their intrinsic analgesic properties, show a stimulant effect on respiration, which offsets the depressant activities of morphine and analogs thereof.

The combination within the scope of this application with respect to the morphine-type component is not limited to morphine alone. It is intended that morphine derivatives and other substances having morphine-like activity be included as components of the combination, such as, for example, codeine, ethyl-morphine, α -isomorphine, isocodeine, β -isomorphine, allopseudo-codeine, γ -isomorphine, monoacetylmorphine, heterocodeine, dihydromorphinone, dihydrocodeinone, dihydrodesoxy-morphine-D, tetrahydrodesoxymorphine, methyl dihydromorphinone, ethyl dihydromorphinone, dihydrohydroxy-codeinone and the like, or mixtures of such compounds or plant extracts containing alkaloids of the above type, as well as synthetic analogs having structural features of the morphine molecule, such as meperidine, ketobemidone, methadone, 3-methoxy-N-methyl-morphinane, 3-hydroxy-N-methyl-morphinane and the like, or ther-

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apeutically acceptable acid addition salts of such compounds.

The 2-amino-indane compounds are primarily those of the formula:



in which R₁ represents hydrogen or methyl, and R₂ stands for hydrogen or halogeno, particularly fluoro, as well as chloro and the like, or the therapeutically acceptable acid addition salts of such compounds.

The ratio of the morphine-like analgesic substance to the 2-amino-indane compound in the compositions of this invention appears to be from about 1:0.1 to about 1:5, i.e. per one part of the morphine-type analgesic about 0.1 to about 5 parts of the 2-amino-indane compound are required; the optimal ratio being about 1:1, i.e. per one part of the morphine analgesic about one part of the 2-amino-indane compound is present.

The actual dose administered will vary widely depending upon the age, weight and condition of the patient, as well as the character of the morphine-type component used in the composition. For example, in the case of morphine, a quantity of about 0.005 g. of morphine or salt thereof, e.g. sulfate and the like, and from about 0.002 g. to about 0.005 g. of the 2-amino-indane compound, e.g. 2-amino-indane and the like, or salt thereof, e.g. hydrochloride and the like, appears to be adequate. The drugs may be administered in combination in a single dosage unit, separately in single dosage units or successively—for example, a dose of the morphine-type analgesic, followed by a dose of the 2-amino-indane compound.

Depending upon the nature of the morphine-type analgesic component employed, the 2-amino-indane compound may either potentiate the degree of analgesia obtainable with the morphine-type component or it may induce analgesia at dose levels where no analgesia is obtainable, if the morphine-type drug above is administered. For example, ketobemidone shows a significant degree of analgesia in doses of 0.005 g. If this dose is combined with from about 0.005 g. to about 0.01 g. of 2-amino-indane hydrochloride, there is a marked potentiation of the analgesic effect. Codeine, on the other hand, shows only weak analgetic effects in doses of 0.01 g., but when combined with from about 0.005 g. to about 0.01 g. of 2-amino-indane hydrochloride or any other of the above-mentioned 2-amino-indane compounds, it shows a significant degree of analgesia. In doses of 0.02 g. meperidine (as the hydrochloride) shows only a weak analgetic effect, but when combined at this dose level with about 0.005 g. to about 0.01 g. of 2-amino-indane hydrochloride or any other of the above-mentioned 2-amino-indane compounds, there is a marked potentiation of analgesia.

In preparing suitable, physiologically acceptable dosage unit forms, any one of a wide variety of preparations may be compounded, as, for example, tablets, capsules, dragees, powders, etc. In addition to the active ingredient, there may be present additional substances commonly employed in the pharmaceutical art for preparing therapeutic compositions, as for example, excipients, binders, fillers and other inert ingredients. The 2-amino-indane compounds are preferably used in the form of their therapeutically acceptable acid addition salts, e.g. the hydrochlorides, sulfates, phosphates, tartrates, citrates and the like; the morphine-type compounds may also be used in the form of their salts, such as hydrochlorides, sulfates, nitrates and the like.

A convenient oral form for administration is the tablet,

capsule, dragee and the like; powders and the like may also be used. Generally, orally applicable forms contain from about 0.001 g. to about 0.03 g., preferably from about 0.005 g. to about 0.02 g., of the morphine-type analgesic (depending on the type of analgesic effect exerted by the latter) and of from about 0.001 g. to about 0.03 g., preferably from about 0.002 g. to about 0.01 g., of the 2-amino-indane compound per single dosage unit.

Fillers and binders which are commonly employed in the art may be used in formulating the orally applicable forms. Examples of these materials are starches, e.g. corn starch and the like, lactose, stearic acid, magnesium stearate, talc, tragacanth, acacia and the like. The quantities of these ingredients may vary widely and depend, to a large degree, upon the kind, i.e. soft or hard, and the size of tablet which is required. Encapsulation may also be effected using the same excipients as those used for tablets. As has been indicated above, the compounding is generally effected in the same manner as that normally employed in the art. Any compatible colors, approved and certified under the provisions of the Federal Food, Drug and Cosmetic law may be used for esthetic purposes or as a means of identification.

For example, a preferred orally applicable form, e.g. tablet and the like, contains about 0.005 g. of morphine (if desired, in the form of a therapeutically acceptable acid addition salt thereof, e.g. sulfate and the like) and about 0.005 g. to about 0.01 g. of 2-amino-indane (preferably in the form of a therapeutically acceptable acid addition salt thereof, e.g. hydrochloride and the like) per single dosage unit.

The present invention also includes within its scope a method for the alleviation of pain, which comprises administering to a host requiring alleviation of pain a pharmaceutical composition consisting essentially of (a) a morphine-type analgesic as defined hereinbefore, (b) a 2-amino-indane compound, and (c) an inert, pharmaceutical carrier. Preferred ingredients of such composition are those previously mentioned; the administration of a combination of morphine (if desired, in the form of a therapeutically acceptable acid addition salt, e.g. sulfate and the like) and 2-amino-indane (preferably in the form of a therapeutically acceptable acid addition salt thereof, e.g. hydrochloride and the like) represents according to the method of this invention a preferred treatment of a host requiring pain relief.

As specific examples of formulations suitable for administration may be given the following:

Example 1

0.05 g. of morphine sulfate is mixed with 0.04 g. of 2-amino-indane hydrochloride and triturated with 2.0 g. of lactose. The mixture is divided into 10 equal dosage forms and administered orally as a powder.

Example 2

2.0 g. of morphine sulfate is mixed with 2.0 g. of 2-amino-indane hydrochloride, and the mixture is triturated with 3.0 g. of tragacanth and then with 120.0 g. of lactose. The mass is granulated with 50 percent aqueous ethanol, passed through a No. 10 screen, dried and passed through a screen of suitable mesh. 4.0 g. each of talcum and corn starch and 0.7 g. of magnesium stearate are worked in. The mixture is sifted and compressed with a punch of suitable size to make tablets containing 0.005 g. of morphine sulfate and 0.005 g. of 2-amino-indane hydrochloride.

Example 3

0.05 g. of morphine sulfate is mixed with 0.05 g. of 2-amino-2-methyl-indane hydrochloride and triturated with 2.0 g. of lactose. The mixture is divided into 10 equal dosage forms and administered orally as a powder.

Example 4

2.0 g. of morphine sulfate is mixed with 2.0 g. of 2-amino-2-methyl-indane hydrochloride, and the mixture is triturated with 3.0 g. of tragacanth and then with 120.0 g. of lactose. The mass is granulated with 50 percent aqueous ethanol, passed through a No. 10 screen, dried thoroughly without heat and passed through a screen of suitable mesh. 4.0 g. each of talcum and corn starch and 0.7 g. of magnesium stearate are worked in. The mixture is sifted and compressed with a punch of suitable size to make tablets containing 0.005 g. of morphine sulfate and 0.005 g. of 2-amino-2-methyl-indane hydrochloride.

In the above examples, morphine sulfate may be replaced by other morphine-type alkaloids or salts thereof e.g. codeine sulfate and the like, or by synthetic analgesics having morphine-type effects or salts thereof, e.g. ketobemidone hydrochloride, merperidine hydrochloride and the like; the 2-amino-indane hydrochloride or the 2-amino-2-methyl-indane hydrochloride may be replaced by 2-amino-5-fluoro-indane hydrochloride and the like.

The 2-amino-indane compounds used in the compositions of this invention may be prepared as follows:

Example A

A solution of 14.8 g. of 2-indanone in 75 ml. of pyridine is added to a solution of 9.35 g. of hydroxylamine hydrochloride in 50 ml. aqueous ethanol, and the mixture is allowed to stand for two days at room temperature. The precipitate, formed after being poured onto ice-water, is filtered off and then air dried to yield the 2-oximino-indane, M.P. 150–154° C.; yield: 92.3%.

A solution of 7.6 g. of 2-oximino-indane in a mixture of 150 ml. of ethanol and 21.75 ml. of a 7.1 N solution of hydrogen chloride in ethanol is treated with hydrogen in the presence of 0.75 g. of a palladium catalyst (20 percent palladium on charcoal). The catalyst is filtered off, the filtrate is concentrated and the resulting 2-amino-indane hydrochloride is recrystallized from a mixture of ethanol and ethyl acetate, M.P. 233–240° C.

The free base may be obtained from the hydrochloride by treating an aqueous solution of the latter with aqueous ammonia and extracting the liberated 2-amino-indane with diethyl ether. From the free base other salts, such as the 2-amino-indane sulfate, 2-amino-indane phosphate, 2-amino-indane D-tartrate, 2-amino-indane maleate, 2-amino-indane methane sulfonate, 2-amino-indane p-toluene sulfonate and the like, can be prepared by reacting 2-amino-indane with the appropriate acids, such as sulfuric, phosphoric, D-tartaric, maleic, methane sulfonic, p-toluene sulfonic acid and the like.

Example B

To a refluxing solution of 74.0 g. of potassium cyanide in 125 ml. of water, diluted with about 200 ml. of ethanol is added 135 g. of α,α' -dibromo-o-xylene in portions. The reaction mixture is refluxed for an additional thirty minutes and is then diluted with water until the product oils out. The organic material is extracted with diethyl ether, the extract solution is washed with water, dried and then evaporated. The solid residue is recrystallized from ethanol to yield α,α' -dicyano-o-xylene, M.P. 58–50° C.; yield: 57 g.

A solution of 20.0 g. of α,α' -dicyano-o-xylene in 800 ml. of ethanol is heated to reflux, using a wide-bore condenser. 20.0 g. of sodium is added through the condenser as rapidly as possible, while heating is interrupted. After cooling, the reaction mixture is diluted with ethanol and then acidified with hydrochloric acid. The solid material is filtered off, the ethanol is evaporated under reduced pressure, and the remaining solution is made basic with aqueous ammonia while cooling. The organic material is extracted with diethyl ether, the ether solution is separated, washed, dried and evaporated. The remain-

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ing residue is cooled and made basic with aqueous ammonia; the organic material is extracted into diethyl ether, the extract solution is washed, dried and evaporated. The remaining oil is distilled to yield 5.5 g. of 2-amino-2-methyl-indane, B.P. 103–105°/12 mm.

A small portion of the free base is converted into 2-amino-2-methyl-indane hydrochloride, which melts at 225–232° after recrystallization from a mixture of ethanol and diethyl ether. Other acid addition salts, such as the sulfate, phosphate, D-tartrate, maleate, methane sulfonate, p-toluene sulfonate and the like, 2-amino-2-methyl-indane may be prepared as shown in Example A.

Example C

A mixture of 20 g. of 4-fluoro-benzaldehyde, 43 g. of malonic acid and 34 ml. of pyridine is heated on the steam bath for four hours. The reaction mixture is then poured onto ice and acidified with aqueous hydrochloric acid. The resulting 4-fluoro-cinnamic acid is collected, washed with water and air-dried, M.P. 207–210°; yield: ca. 90 percent.

A mixture of 22.0 g. of 4-fluoro-cinnamic acid, 220 ml. of 90 percent ethanol and 1.2 g. of palladium (10 percent on charcoal) is shaken at room temperature with hydrogen under about 4 atmospheres pressure. The uptake of one mol of hydrogen is complete after about ninety minutes. The catalyst is filtered off, and then the filtrate is evaporated to dryness under reduced pressure to yield the β -(4-fluoro-phenyl)-propionic acid, M.P. 88–90°; yield: 20 g.

A mixture of 21.5 g. of β -(4-fluoro-phenyl)-propionic acid in 215 g. of polyphosphoric acid is vigorously stirred at 85–87° for twenty-five minutes. The hot reaction mixture is poured onto ice, and the organic material is extracted with diethyl ether. The organic solution is washed with water, aqueous sodium hydrogen carbonate and again with water, dried over magnesium sulfate and evaporated to dryness. The resulting 6-fluoro-indan-1-one is purified by recrystallization from hexane, M.P. 55–57°; yield: 13.45 g.

To a solution of 4.0 g. of 6-fluoro-indan-1-one in 10 ml. of ethanol is added 4.0 g. of n-pentyl nitrite while maintaining a temperature of 15°. The mixture is then treated dropwise with 1.0 ml. of concentrated hydrochloric acid while keeping the temperature below 45°. After completion of the addition, the reaction mixture is stirred at 45° for thirty minutes and then cooled; 3.05 g. of the desired 6-fluoro-2-nitroso-indan-1-one is collected, M.P. 334–337° (decomposition).

A mixture of 6-fluoro-2-nitroso-indan-1-one, 0.95 ml. of concentrated sulfuric acid, 50 ml. of glacial acetic acid and 0.1 g. of palladium black is shaken for eighteen hours with hydrogen about 3 atmospheres pressure, while maintaining a temperature of 60°. The catalyst is filtered off; the filtrate is neutralized by adding aqueous sodium hydroxide and evaporated to dryness under reduced pressure. The residue is taken up in a minimum amount of water, the aqueous solution is made basic with aqueous ammonia, and the organic material is extracted with diethyl ether. The organic solution is washed, dried and evaporated to yield an oily residue which is treated with ethanolic hydrogen chloride; and the desired 2-amino-5-fluoro-indane hydrochloride is collected and recrystallized from ethanol, M.P. 250–253°; yield 1.8 g.

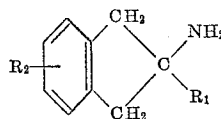
What is claimed is:

1. An analgesic composition consisting essentially of (a) an analgesic of the morphine-type, (b) a 2-amino-indane compound, and (c) an inert carrier, the ratio between the morphine-type analgesic and the 2-amino-indane compound being from about 1:0.1 to about 1:5.

2. An analgesic composition as claimed in claim 1, wherein the morphine-type analgesic is selected from a member of the group consisting of morphine, codeine, ethylmorphine, α -isomorphine, isocodeine, β -isomorphine, alloperidocodine, γ -isomorphine, monoacetylmorphine,

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heterocodeine, dihydromorphinone, dihydrocodeinone, dihydrodesoxymorphine-D, tetrahydrodesoxymorphine, methyl-dihydromorphinone, ethyldihydromorphinone, dihydrocodeinone, meperidine, ketobemidone, methadone, 3-methoxy-N-methyl-morphinane, and 3-hydroxy-N-methyl-morphinane, and the 2-amino-indane compound is selected from a member of the group consisting of a compound of the formula

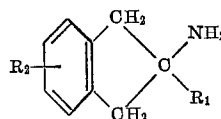


in which R₁ stands for a member of the group consisting of hydrogen and methyl, R₂ stands for a member of the group consisting of hydrogen and halogeno, and therapeutically acceptable acid addition salts thereof.

3. An analgesic composition as claimed in claim 1, wherein the morphine-type analgesic is a therapeutically acceptable acid addition salt of morphine, and the 2-amino-indane compound is a therapeutically acceptable acid addition salt of 2-amino-indane.

4. An analgesic composition containing from about 0.001 g. to about 0.03 g. of an analgesic of the morphine-type and from about 0.001 g. to about 0.03 g. of a 2-amino-indane compound per dosage unit.

5. An analgesic composition as claimed in claim 4, wherein the morphine-type analgesic is selected from a member of the group consisting of morphine, codeine, ethylmorphine, γ -isomorphine, monoacetylmorphine, heterocodeine, dihydromorphinone, dihydrocodeinone, dihydrodesoxymorphine-D, tetrahydrodesoxymorphine, methyl-dihydromorphinone, ethyldihydromorphinone, dihydrocodeinone, meperidine, ketobemidone, methadone, 3-methoxy-N-methyl-morphinane, and 3-hydroxy-N-methyl-morphinane, and the 2-amino-indane compound is selected from a member of the group consisting of a compound of the formula



in which R₁ stands for a member of the group consisting of hydrogen and methyl, and R₂ represents a member of the group consisting of hydrogen and halogeno, and therapeutically acceptable acid addition salts thereof.

6. An analgesic composition as claimed in claim 4, wherein the morphine-type analgesic is a therapeutically acceptable acid addition salt of morphine, and the 2-amino-indane compound is a therapeutically acceptable acid addition salt of 2-amino-indane.

7. An analgesic composition containing about 0.005 g. of a therapeutically acceptable acid addition salt of morphine and from about 0.002 g. to about 0.005 g. of a therapeutically acceptable acid addition salt of 2-amino-indane per dosage unit.

8. An analgesic composition as claimed in claim 7, wherein morphine sulfate is the therapeutically acceptable acid addition salt of morphine and 2-amino-indane hydrochloride is the therapeutically acceptable acid addition salt of 2-amino-indane.

9. A method for the alleviation of pain, which comprises administering to a host requiring alleviation of pain an analgesic composition consisting essentially of (a) an analgesic of the morphine-type, (b) a 2-amino-indane compound, and (c) an inert carrier, the ratio between the morphine-type analgesic and the 2-amino-indane compound being about 1:0.1 to about 1:5.

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