

[54] PHENOL COMPOUNDS IN TREATING
PAIN, FEVER AND INFLAMMATION

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[56]

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[57]

ABSTRACT

The invention relates to a method of treating inflammation employing certain aminomethylphenol compounds and to pharmaceutical compositions thereof.

9 Claims, No Drawings

PHENOL COMPOUNDS IN TREATING PAIN, FEVER AND INFLAMMATION

SUMMARY OF THE INVENTION

This invention relates to the use of aminomethylphenols containing halogen and alkyl substituents as medicinal agents. These compounds exhibit anti-inflammatory activity and are particularly useful as topical and systemic agents.

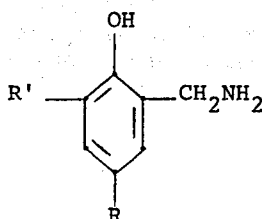
BACKGROUND OF THE INVENTION

There has been much research carried on in the past for development of anti-inflammatory drugs. As a result, a great many new drugs have been synthesized. Most of these have been steroids of the 11-oxygenated pregnane series. These, while highly effective, have the drawback of causing many side effects. There has also been a concentrated effort in anti-inflammatory research in indole, indenes and phenylacetic acids among others with the result of many useful drugs. We have found that certain aminomethylphenols also are valuable anti-inflammatory agents.

DESCRIPTION AND PREFERRED EMBODIMENTS

This invention is directed to the use of known aminomethylphenol compounds as anti-inflammatory agents. The invention is also directed to pharmaceutical compositions employing these compounds. These compounds and their method of preparation are generally known from German publication Ser. No. 2,163,908, filed Dec. 22, 1971.

The treatment of inflammation in accordance with the method of the present invention is accomplished by topically, orally, rectally or parenterally administering to patients the aminomethylphenols of the following formula:



wherein R is C₃₋₇ loweralkyl, such as propyl, isopropyl, sec-butyl, t-butyl, t-amyl and the like, but especially t-butyl and isopropyl and R' is halogen, such as chloro, bromo, fluoro and iodo, and especially iodo and chloro, in a non-toxic pharmaceutically acceptable carrier. Also included are their non-toxic pharmaceutically acceptable salts, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, methanesulfonic, isethionic acid and the like. Salts may also be prepared from the alkali metal bases such as sodium hydroxide, potassium hydroxide and the like.

The non-toxic pharmaceutical carrier may be, for example, either a solid or a liquid. Exemplary of solid carriers are lactose, corn starch, gelatin, talc, stearic acid, magnesium stearate, terra alba, sucrose, agar, pectin and acacia. Exemplary of liquid carriers are peanut oil, olive oil, sesame oil, propylene glycol, glycerine, ethanol and water. Similarly, the carrier or diluent may include a time delay material such as glyc-

eryl monostearate or glyceryl distearate alone or with a wax.

Several pharmaceutical forms of the therapeutically useful compositions can be used. For example, if a solid carrier is used, the compositions may take the form of tablets, capsules, powders, troches or lozenges, prepared by standard pharmaceutical techniques. If a liquid carrier is used, the preparation may be in the form of a soft gelatin capsule, a syrup, an aqueous solution or a liquid suspension. Suppositories may be prepared in a conventional manner by mixing the compounds of this invention with a suitable nonirritating excipient which is solid at room temperature, but liquid at the rectal temperature. Such materials are cocoa butter and polyethylene glycol.

The active compounds are administered in an amount sufficient to treat inflammation; that is, to reduce inflammation. Advantageously, the compositions will contain the active ingredient in an amount of from about 0.1 mg. to 50 mg. per kg. body weight per day (5 mg. to 3.5 g. per patient per day), preferably from about 1 mg. to 15 mg. per kg. body weight per day (50 mg. to 1 g. per patient per day).

In a particularly preferred aspect of this invention, the aminomethylphenols are used as topical anti-inflammatory agents and are particularly effective in topical treatment of dermatological disorders and like conditions, such as dermatitis (actinic, atopic, contact, eczematoid, seborrheic and stasis), dermatitis herpetiformis, lichen planus, neurodermatitis, intertrigo, lichen simplex chronicus, and pruritus, as well as for topical treatment of inflammation of the respiratory and intestinal mucosa such as allergic rhinitis, bronchitis, bronchial asthma, bronchiectasis, colitis and the like. These aminomethylphenols are ordinarily administered in the form of a pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable carrier adapted for topical administration. These topical pharmaceutical compositions may be in the form of a cream, ointment, gel or aerosol formulation adapted for application to the skin for treatment of dermatoses; or it may be in the form of a solution, suspension or aerosol adapted for topical spray application to respiratory passages for treatment of nasal allergies, bronchial inflammation, and the like; or in the form of suppositories or enclosed in enteric capsules for treatment of intestinal inflammations. For treatment of dermatological disorders, these topical pharmaceutical compositions containing the aminomethylphenols ordinarily include about 0.01 to 2 percent, preferably about 0.5 percent, of the active compound in admixture with 99.75 to 99.99 percent (preferably 99.90 percent) of gel vehicle comprising water, at least one organic solvent, and at least one thickening agent. The water ordinarily constitutes from about 8 to 18 percent of the gel vehicle, preferably about 13 percent. The organic solvent ordinarily constitutes about 60 to 90 percent of the gel vehicle. Representative solvents are ethyl alcohol, isopropyl alcohol, propylene glycol, glycerine, 2-octyldodecanol and N-methylpyrrolidine, and preferably isopropyl alcohol; propylene glycol mixtures at a ratio of 0.5 to 0.6 parts isopropyl alcohol to 1.0 parts propylene glycol. The solubility of the aminomethylphenol compounds in the solvent system selected should be such as to obtain maximum partitioning of the active compound from the vehicle to the skin. The thickening agent, preferably hydroxyethyl cellulose, hydroxypropyl cellulose,

and the like, ordinarily constitutes from 0.5 to 4.0 percent of the gel vehicle. Optionally, a stabilizing agent, such as disodium edetate, sodium citrate, dipotassium edetate, citric acid, and the like, in the proportion of about 0.02 to 0.5 percent of the gel vehicle may be employed, if desired.

A preferred topical pharmaceutical composition is prepared as follows: About 2.60 g. of hydroxypropyl cellulose is added to a solution of 0.05 g. of disodium edetate in 13.00 g. purified water while agitating the mixture and maintaining the temperature at about 60°C, and the agitation is continued until the hydroxypropyl cellulose is completely dispersed and wetted. To the resulting dispersed mixture is added, with agitation, a solution containing 0.1 g. of, for example, 2-aminomethyl-4-t-butyl-6-fluorophenol hydrochloride dispersed in a mixture of 30.00 g. of anhydrous isopropyl alcohol and 54.25 g. of propylene glycol. The resulting gel mixture is stirred vigorously at room temperature for a period of approximately 15 minutes thereby forming a pharmaceutical composition adapted for the treatment of topical anti-inflammatory conditions.

Various tests in animals have been carried out to show the ability of the compounds described herein to exhibit reactions that can be correlated with anti-inflammatory activity in humans. One such test used is the mouse ear test which is known to correlate well with anti-inflammatory activity in humans and is a standard test used to determine anti-inflammatory activity.

The following examples are given by way of illustration:

EXAMPLE 1

A mixture of 250 parts of 2-aminomethyl-4-t-butyl-6-bromophenol and 25 parts of lactose is granulated with suitable water, and to this is added 100 parts of maize starch. The mass is passed through a 16 mesh screen. The granules are dried at a temperature below 60°C. The dry granules are passed through a 16 mesh screen and mixed with 3.8 parts of magnesium stearate. They are then compressed into tablets suitable for oral administration.

25, 100 or 500 parts of 2-aminomethyl-4-t-butyl-6-bromophenol may be used in place of 250 parts above to produce tablets suitable for oral administration according to the method of this invention.

EXAMPLE 2

A mixture of 50 parts of 2-aminomethyl-4-t-butyl-6-chlorophenol, 3 parts of the calcium salt of lignin sulfonic acid and 237 parts of water is ball-milled until the size of substantially all of the particles is less than 10 microns. The suspension is diluted with a solution containing 3 parts of sodium carboxymethyl cellulose and 0.9 parts of the butyl ester of p-hydroxybenzoic acid in 300 parts of water. There is thus obtained an aqueous suspension suitable for oral administration for therapeutic purposes.

2-Aminomethyl-4-t-butyl-6-iodophenol is used in place of the 6-chlorophenol compound in the above example to obtain a suspension suitable for oral administration.

EXAMPLE 3

A mixture of 250 parts of 2-aminomethyl-4-isopropyl-6-chlorophenol, 200 parts of maize starch and 30 parts of alginic acid is mixed with a sufficient quantity of 10% aqueous paste of maize starch, and granulated.

The granules are dried in a current of warm air, and the dry granules are then passed through a 16-mesh screen, mixed with 6 parts of magnesium stearate and compressed into tablet form to obtain tablets suitable for oral administration.

Similar results are obtained by employing 2-aminomethyl-4-isopropyl-6-iodophenol in place of the ethylamino compound in the above example.

EXAMPLE 4

A mixture of 500 parts of 2-aminomethyl-4-t-amyl-6-iodophenol, 60 parts maize starch and 20 parts of gum acacia is granulated with a sufficient quantity of water. The mass is passed through a 12-mesh screen and the granules are dried in a current of warm air. The dry granules are passed through a 16-mesh screen, mixed with 5 parts of magnesium stearate and compressed into tablet form suitable for oral administration.

Similar results are obtained by employing 2-aminomethyl-4-t-amyl-6-chlorophenol in place of the allylamino compound in the above example.

EXAMPLE 5

1. Tablets — 10,000 scored tablets for oral use, each containing 500 mg. of active ingredient are prepared from the following ingredients:

	Gm.
2-aminomethyl-4-propyl-6-chlorophenol	5000
Starch, U.S.P.	350
Talc, U.S.P.	250
Calcium stearate	35

The chlorophenol is granulated with a 4% w/v. aqueous solution of methyl cellulose U.S.P. (1500 cps.). To the dried granules is added a mixture of the remainder of the ingredients and the final mixture compressed into tablets of proper weight.

2. Capsules — 10,000 two-piece hard gelatin capsules for oral use, each containing 250 mg. of active ingredient are prepared from the following ingredients:

	Gm.
2-Aminomethyl-4-t-butyl-6-bromophenol	2500
Lactose, U.S.P.	1000
Starch, U.S.P.	300
Talc, U.S.P.	65
Calcium stearate	25

The bromophenol compound is mixed with the starch lactose mixture followed by the talc and calcium stearate. The final mixture is then encapsulated in the usual manner. Capsules containing 10, 25, 50 and 100 mg. of active ingredient are also prepared by substituting 100, 250, 500 and 1000 gm. for 2500 gm. in the above formulation.

3. Soft elastic capsules — One-piece soft elastic capsules for oral use, each containing 500 mg. of active material are prepared in the usual manner by first dispersing the active material in sufficient corn oil to render the material capsulatable.

4. Aqueous suspension — An aqueous suspension for oral use containing in each 5 ml., 1 gm. of active ingredient is prepared from the following ingredients:

	Gm.
2-Aminomethyl-4-t-butyl-6-iodophenol	2000
Methylparaben, U.S.P.	7.5

-continued

	Gm.
Propylparaben, U.S.P.	2.5
Saccharin sodium	12.5
Glycerin	3000
Tragacanth powder	10
Orange oil flavor	10
F.D. & C. orange dye	7.5
Deionized water, q.s. to 10,000 ml.	

EXAMPLE 6

Gel Formulation

0.1 mg. disodium edetate
1.30 mg. of purified H₂O
300 mg. isopropanol
26 mg. hydroxypropyl cellulose
q.s.a.d. 1 gm. propylene glycol
1.09 mg. 2-aminomethyl-4-t-butyl-6-bromophenol hydrochloride

EXAMPLE 7

Ointment Formulation

50 mg. wool alcohols B.P.
150 mg. amichol C
350 mg. wax white Be square 170/175°C
q.s.a.d. 1 gm. isopropyl myristate
1.09 mg. 2-aminomethyl-4-isopropyl-6-iodophenol hydrochloride
.4% citrate acid anhydrous
0.5% sodium phosphate dibasic anhydrous

EXAMPLE 8

2-Aminomethyl-4-isopropyl-6-chlorophenol hydrochloride

2-Chloro-4-isopropylphenol (8.35 g., 0.05 mole) is dissolved in a mixture of acetic acid (50 ml.) and 96% sulfuric acid (5 ml.). Finely powdered N-hydroxymethyl-2-chloroacetamide (6.15 g., 0.05 mole) is added gradually with stirring at about 20°C. The mixture is stirred for 2.5 hours additionally and then is poured into 300 ml. of cold water. The gum that separates is extracted with ether. The ether extract is washed with water and with salt brine, dried with magnesium sulfate and evaporated to dryness. The residue is refluxed in a mixture of 95% ethanol (25 ml.) and 12 N hydrochloric acid (10 ml.) for 2.5 hours. The product that separates on cooling is crystallized from ethanol - 12 N hydrochloric acid (3:2) to obtain 2-aminomethyl-4-isopropyl-6-chlorophenol hydrochloride, 5.8 g., m.p. 241°-242°C.

Analysis: Calc.: C, 50.86; H, 6.40; N, 5.93; Found: C, 50.53; H, 6.46; N, 5.98.

Following the procedure in Example 8 above but using an equivalent amount of 2-chloro-4-t-amylphenol in place of 2-chloro-4-isopropylphenol, there is obtained an equivalent amount of 2-aminomethyl-4-t-amyl-6-chlorophenol hydrochloride.

EXAMPLE 9

2-Aminomethyl-4-isopropyl-6-iodophenol hydrochloride

Step 1: 2-Iodo-4-isopropylphenol

4-Isopropylphenol (27.2 g., 0.20 mole) is dissolved in acetic acid (100 ml.). Iodine monochloride (32.5 g., 0.20 mole) in acetic acid (50 ml.) is then added slowly. The dark mixture is refluxed for 6 hours, cooled and poured into cold water (1 l.) containing a little sodium

bisulfite. The black oil that separates is extracted with ether and the extract is washed with water and salt brine and dried over magnesium sulfate. The ether is evaporated and the residue is purified by distillation to obtain 2-iodo-4-isopropylphenol (26 g.), m.p. 137°-140°C (15 mm.).

Analysis: Calc.: C, 41.89; H, 4.23; Found: C, 41.69; H, 4.62.

Step 2: 2-Aminomethyl-4-isopropyl-6-iodophenol hydrochloride

2-Iodo-4-isopropylphenol (13.1 g., 0.05 mole) is dissolved in a mixture of acetic acid (50 ml.) and 96% sulfuric acid (5 ml.) and powdered N-hydroxymethyl-2-chloroacetamide (6.15 g., 0.05 mole) is added during 10 minutes with stirring at 20°C. The solution is stirred for 2.5 hours and then added to 300 ml. of water. The crude solid is collected (18 g.) and refluxed in ethanol (25 ml.)-hydrochloric acid (10 ml.) for 2 hours. The solid (7.5 g.) that separates on cooling; namely, 2-aminomethyl-4-isopropyl-6-iodophenol hydrochloride, is purified by crystallization from ethanol - 12 N hydrochloric acid (7:3) to obtain 2-aminomethyl-4-isopropyl-6-iodophenol hydrochloride (7 g.), m.p. 211°-212°C, dec.

Analysis: Calc.: C, 36.66; H, 4.62; N, 4.28; Found: C, 36.51, H, 4.54, N, 4.14.

EXAMPLE 10

2-Aminomethyl-4-t-amyl-6-iodophenol hydrochloride

Step 1: 2-Aminomethyl-4-t-amylphenol hydrochloride

A mixture of 4-t-amylphenol (32.8 g., 0.20 mole), N-hydroxymethyl-2-chloroacetamide (24.6 g., 0.20 mole) in acetic acid (200 ml.) and 96% sulfuric acid (20 ml.) is stirred at 20°C for 12 hours and then poured into cold water (1 l.). The solid that separates is extracted with ether and the ether extract is washed with water and salt brine and evaporated to dryness. The oily residue is dissolved in a mixture of 12 N hydrochloric acid (100 ml.) and ethanol (100 ml.). The mixture is refluxed for 7 hours. The mixture then is evaporated to dryness under reduced pressure. The residue is triturated with dry ether to obtain a sticky white solid that is dissolved in hot ethanol (50 ml.) and precipitated in the cold by addition of ether (800 ml.). The solid is then crystallized from ethanol - 12 N hydrochloric acid (1:10) to obtain 2-aminomethyl-4-t-amylphenol hydrochloride (17 g.), m.p. 191°-192°C.

Analysis: Calc.: C, 62.73; H, 8.77; N, 6.10; Found: C, 62.80; H, 8.76; N, 6.21.

Step 2: 2-Aminomethyl-4-t-amyl-6-iodophenol hydrochloride

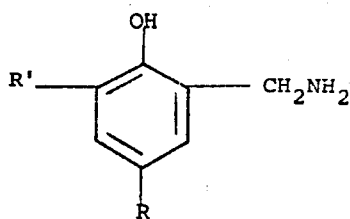
2-Aminomethyl-4-t-amylphenol hydrochloride (4.6 g., 0.02 mole) is dissolved in water (15 ml.) and a solution of iodine monochloride (3.28 g.) in water (5 ml.) is added. The mixture is kept for 3 hours and then cooled to -10°C. The solid that separates is crystallized from ethanol - 12 N hydrochloric acid (1:10) to obtain 2-aminomethyl-4-t-amyl-6-iodophenyl hydrochloride (4.15 g.), m.p. 203°-204°C, dec.

Analysis: Calc.: C, 40.53; H, 5.38; N, 3.94; Found: C, 40.77; H, 5.31; N, 3.97.

What is claimed is:

1. A method of treating a condition exhibiting at least one of the symptoms of pain, fever and inflammation which comprises the administration to a patient in need of such treatment a therapeutically effective amount of a compound of the formula:

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wherein R is C₃₋₇ loweralkyl and R' is halogen, or the non-toxic pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein the compound is 2-aminomethyl-4-t-butyl-6-chlorophenol, or the hydrochloride salt thereof.

3. The method of claim 1 wherein the compound is 2-aminomethyl-4-t-butyl-6-iodophenol, or the hydrochloride salt thereof.

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4. The method of claim 1 wherein the compound is 2-aminomethyl-4-t-butyl-6-bromophenol, or the hydrochloride salt thereof.

5. The method of claim 1 wherein the compound is 2-aminomethyl-4-t-butyl-6-fluorophenol, or the hydrochloride salt thereof.

6. The method of claim 1 wherein the compound is 2-aminomethyl-4-t-amyl-6-chlorophenol, or the hydrochloride salt thereof.

7. The method of claim 1 wherein the compound is 2-aminomethyl-4-t-amyl-6-iodophenol, or the hydrochloride salt thereof.

8. The method of claim 1 wherein the compound is 2-aminomethyl-4-isopropyl-6-chlorophenol, or the hydrochloride salt thereof.

9. The method of claim 1 wherein the compound is 2-aminomethyl-4-isopropyl-6-iodophenol, or the hydrochloride salt thereof.

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