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ANALGESIC METHODS AND COMPOSITIONS

Perttu V. Laakso, Barrington, Ill., assignor to The Kendall Company, Boston, Mass., a corporation of Massachusetts

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9 Claims. (Cl. 167-65)

This application is a division of parent application Serial No. 132,545, filed August 21, 1961, now U.S. Patent No. 3,185,697, granted May 25, 1965.

This invention relates to a new analgesically active compound and compositions containing the compound suitable for use in the treatment of muscular aches and pains.

Analgesic compositions are topically applied in the treatment of muscular soreness due to muscular bruises, sprains and the like. Although the exact mechanism by which these compositions exert their pain-relieving effect is not fully understood, there is general agreement that the active agents in the analgesic compositions must be capable of passing through the skin and effect a vasodilation in the skin and deeper tissues. It has been shown that vasodilation is brought about by stimulation of nerve fibers which cause a dilating response in the arterioles and precapillary arteriolar sphincters. Capillaries and non-muscular venules do not dilate, but because of the arteriolar dilation have an increase in flow rate with a small accompanying distension. In addition, some capillaries previously devoid of blood become filled.

The increase in the supply and flow of blood removes toxins and metabolites in the treated areas. The new blood in the treated areas also brings in a supply of nutrients. The removal of toxins and metabolites and the supply of nutrients contribute to relief of muscular soreness and pain.

The vasodilating effect of analgesically active compounds is accompanied by an increase in the temperature of the skin and erythemic reaction (redness). These changes of temperature and color of the skin can be observed and serve as a measure of the vasodilatory activity of the analgesically active compounds.

The intensity of the change in skin temperature induced by the compounds should not be so great as to be uncomfortable for the patient. Generally, a chemically induced increase in skin temperature of several degrees is tolerable. A large increase in temperature does not in itself qualify a compound as a suitable ingredient for analgesic compositions. The length of time of the chemically induced vasodilation is of considerable importance.

The new compound of this invention is bicyclo-(2.2.1)-hept-5-ene-2-carbinylnicotinate. This nicotinate ester (occasionally referred to hereafter simply as the bicyclo nicotinate) produces a comfortable sensation of warmth when applied to the skin, producing an increase in temperature of between about 3° F. to 4° F. in the skin within about the first half hour after application. The temperature of the skin then gradually decreases, and after about 3 hours is still approximately 1° F. higher than other comparable skin portions of the body. A condition of erythema remains for as long as 24 hours after application, indicating increased blood flow and supply in the region of the treated area.

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Advantageously, the bicyclo-(2.2.1)-hept-5-ene-2-carbinylnicotinate is substantially less odoriferous than many of the presently commercially used analgesically active compounds.

The bicyclo-(2.2.1)-hept-5-ene-2-carbinylnicotinate may be compounded with various carriers normally used in liniment and balm formulations.

The activity of the bicyclo-(2.2.1)-hept-5-ene-2-carbinylnicotinate as an analgesic compound can be objectively illustrated by the occurrence of erythema and rise in temperature of the skin in the locale of application. This activity and comparison thereof with other compounds is hereinafter illustrated.

Erythema

The chemical tested was applied on the inner aspect of the forearm over a previously marked-out one square inch area. The degree of erythema produced was then evaluated at various intervals according to the following scale:

- 0—no erythema
- 1—slight erythema
- 2—clear erythema
- 3—strong erythema
- 4—very strong erythema.

All observations of erythema intensity were made by the same person in order to make the rating objective. Hyperactive and hypoactive individuals were eliminated from the study. No one individual was used as a test subject in less than 4 days before testing again.

In each of the tests tabulated in Table I the vehicle for the analgesically active compound was a 50% mixture of isopropanol in water. The active compounds were present in an amount 5% by weight of the total mixture. The control was the 50% mixture of isopropanol in water.

TABLE I

Active Compound	Maximum Erythema Value	Duration in Hours ¹	Value at 24 Hours
Methyl Nicotinate.....	2.3	6.0	0
Methyl Salicylate.....	0.5	0
Bicyclo-(2.2.1)-hept-5-ene-2-carbinylnicotinate.....	3.0	7.5	0.6
Control.....	0.0	0.0	0.0

¹ Time after application at which erythema rating at least 1.0.

In all instances the skin remained uncovered. The methyl salicylate (more commonly known as oil of wintergreen) produced only a very minor amount of erythema. The bicyclo nicotinate compound of this invention produced a greater amount of erythema than either of the two commonly used analgesically active compounds: methyl nicotinate and methyl salicylate. Most significantly, however, the bicyclo nicotinate ester produced a greater effect for a much longer period of time than either of the other compounds.

Furthermore, the activity of this bicyclo nicotinate ester is greater than the activity of formulations containing mixtures of methyl nicotinate and methyl salicylate either together or with other ingredients to complement the analgesic function of these two compounds. The liniment solution containing 5% bicyclo-(2.2.1)-hept-5-ene-2-carbinylnicotinate in the isopropanol-water carrier was also compared with several commercial analgesic preparations.