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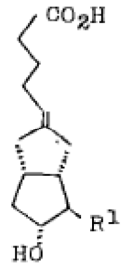
SPECIFICATION

1. Title of the Invention

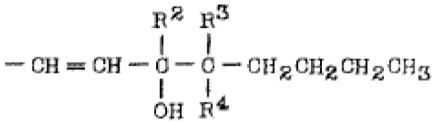
CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

2. Claims

(1) A dicyclohexylamine salt of a methanoprostacyclin derivative expressed by the general formula

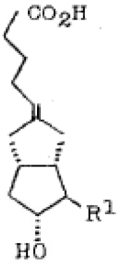


(where R^1 is a trityloxymethyl group, 3-trityloxy-*trans*-1-propenyl group, or the group expressed by the general formula

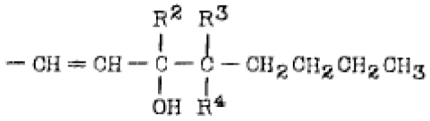


(where R^2, R^3, and R^4 are each a hydrogen atom or a methyl group)).

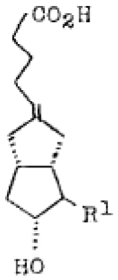
(2) A method for manufacturing a dicyclohexylamine salt of a methanoprostacyclin derivative expressed by the general formula



(where R^1 is a trityloxy group, 3-trityloxy-*trans*-1-propenyl group, or a group expressed by the general formula



(where R^2, R^3, and R^4 are each a hydrogen atom or a methyl group)), characterized in that a mixture of a methanoprostacyclin derivative expressed by the general formula



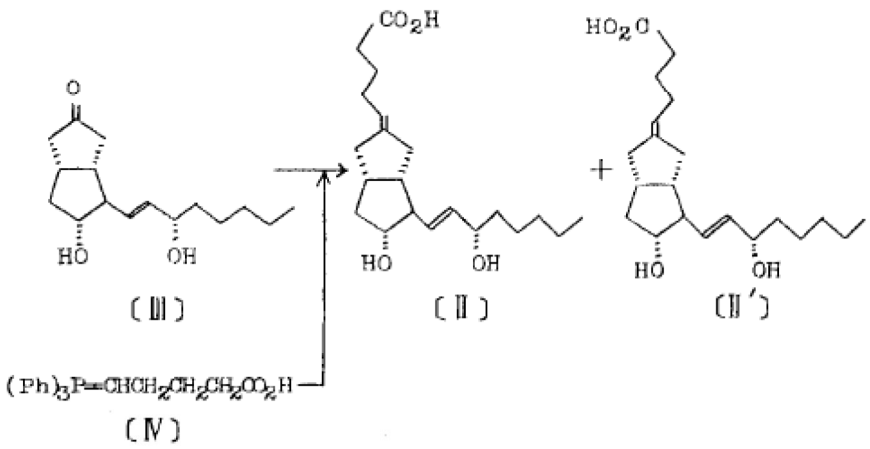
(where R^1 is the same as above) and a 7-Z isomer thereof is converted to a crystalline salt by dicyclohexylamine and is further recrystallized as needed.

3. Detailed Description of the Invention

(Field of Industrial Utilization)

The present invention relates to a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, a manufacturing method thereof, and a purifying method thereof.

Methanoprostacyclin [II] was discovered as a stable derivative of prostacyclin (PGI_2), a natural bioactive substance having a strong blood platelet coagulation-inhibiting action (Tetrahedron Letters, 2607 (1979)). Methanoprostacyclin [II] is by far more chemically stable than prostacyclin, has the same strong blood platelet coagulation-inhibiting action as PGI_2, and is an extremely useful compound in the treatment of arteriosclerosis, heart failure, thrombosis, and the like. Total synthesis of methanoprostacyclin and derivatives thereof has been reported by the inventors and several other groups of researchers, but all the reported methods use a Wittig reaction between a ketone derivative [III] and an ylide derivative [IV], as shown below.



(Ⅲ) (Ⅱ) (Ⅱ′) (Ⅳ)

This reaction has an excellent yield but has a serious drawback of typically producing an unnecessary 7Z isomer [II'] as a byproduct (the generation rate is [II]:[II'] = 7:2, Tetrahedron Letters, 433 (1979)). In addition, the properties of the two are extremely similar (Rf value is 0.14 for 7E, and 0.17 for 7Z; Tetrahedron Letters, 433 (1979)), making separation and purification very difficult. Also, the melting point of this compound is fairly low (68°C to 69°C, Tetrahedron Letters, 3743 (1978)), and crystallization is therefore severely impeded by the admixing of trace impurities.

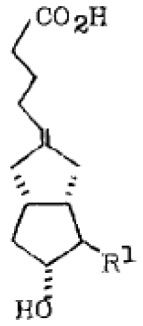
On the other hand, the 7Z isomer [II'] has an extremely low pharmacological activity compared with methanoprostacyclin [II]. For example, the blood platelet coagulation-inhibiting action of II' is about 1/100 of II (Tetrahedron Letters, 433 (1979)).

Thus, establishment of an efficient and industrially viable method of separating isomers of methanoprostacyclin derivatives is essential in the development of these derivatives as pharmaceutical products.

In view of the above, the inventors conducted an examination of various separation and purification methods after achieving success in the synthesis of methanoprostacyclin, and finally succeeded in inventing an extremely simple and industrially viable purification method. The present invention relates to this novel purifying method and to a novel dicyclohexylamine salt of a methanoprostacyclin derivative [I] obtained thereby.

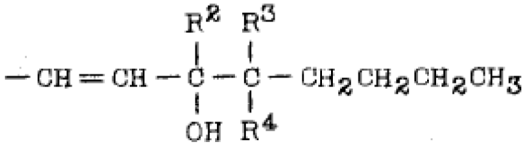
The methanoprostacyclin derivative in which any of R^2, R^3, or R^4 in general formula [I] is a methyl group has excellent blood platelet coagulation-inhibiting action in the same manner as methanoprostacyclin (Japanese Laid-open Patent Application No. 54-119444), and a methanoprostacyclin derivative in which R^1 is a trityloxymethyl group or a 3-trityloxy-*trans*-1-propenyl group is important as an intermediate of methanoprostacyclin synthesis (Japanese Patent Application Nos. 54-29233 and 54-29236).

According to the present invention, a dicyclohexylamine salt of a methanoprostacyclin derivative expressed as methanoprostacyclin derivative [I]



[I]

(where R^1 is a trityloxymethyl group, 3-trityloxy-*trans*-1-propenyl group, or the group expressed by the general formula



(where R^2, R^3, and R^4 are each a hydrogen atom or a methyl group))

can be obtained in the following manner. Specifically, the dicyclohexylamine salt is obtained by mixing a methanoprostacyclin derivative [I] or a methanoprostacyclin derivative [I] containing the corresponding 7Z isomer [I']

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