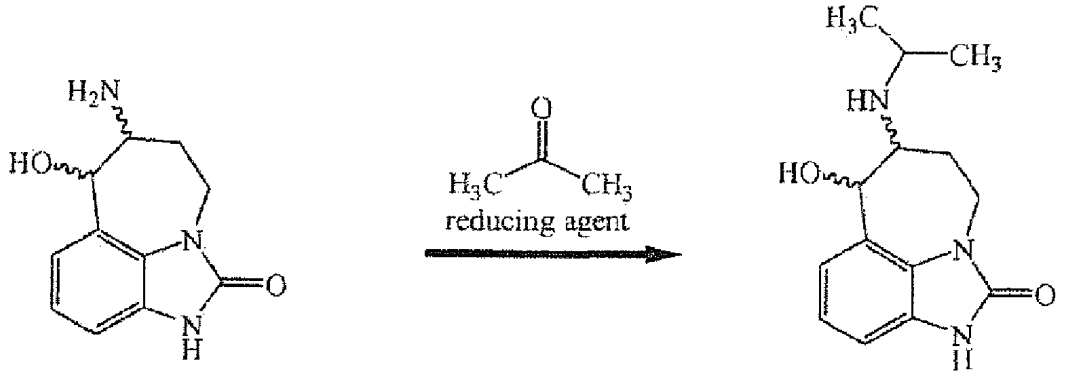
H_2 in the presence of Pd-on-carbon, and, then, after filtration, the hydrogenation product is reacted with sodium borohydride. *See* U.S. Patent 4,585,770, col. 2, line 15 to col 4, line 2; and Example 1, Steps E & F, col. 7, line 38 to col 8, line 3.

[10] U.S. Patent 4,585,770 reports that the *trans* stereoisomers of 6-amino-7-hydroxy-4,5,6,7-tetrahydro-imidazo[4,5,1-jk][1]-benzazepin-2[1H]-one may be alkylated with acetone in the presence of a reducing agent *(e.g.,* an alkali metal borohydride or cyanoborohydride, such as sodium cyanoborohydride) to form racemic *trans* ziipaterol:



racemic *trans*
6-amino-7-hydroxy-4,5,6,7-tetrahydro-imidazo[4,5,1-jk][1]-benzazepin-2[1H]-one

racemic *trans* zilpaterol

See U.S. Patent 4,585,770, col. 2, line 46 to col. 4, line 2; and Example 13, col. 11, lines 41-68.

[11] In view of the importance of zilpaterol and its salts in animal production, there continues to be a need for cost-effective, high-yield processes for making ziipaterol and its salts. The following disclosure addresses this need.

SUMMARY

[12] This disclosure relates to processes for making zilpaterol and salts thereof. Such processes include processes for making zilpaterol and the salts themselves, as well as processes for making compounds that, *inter alia,* may be used as intermediates for making zilpaterol and salts thereof.

[13] Briefly, this disclosure is directed, in part, to a process for making zilpaterol or a salt thereof *(e.g.,* a pharmaceutically acceptable salt). The process comprises making chloro 2,3-dihydro-2-oxo-1 H-benzimidazol-1 -butanoate (or a salt thereof) by a process comprising reacting 4-(2-oxo-2,3-dihydrobenzimidazol-l-yl)butyric acid (or a salt thereof) with at least one chlorinating agent, such as oxalyl chloride, phosgene, and/or triphosgene. Alternatively (or additionally), the process comprises making 4,5-dihydro-imidazo[4,5,1-jk][l]benzazepin-2,6,7[lH]-trione-6-oxime (or a salt thereof) by a process comprising

reacting 8,9-dihydro-2H,7H-2,9a-diazabenzo[cd]azulene-1,6-dione (or a salt thereof) with an inorganic nitrite *(e.g.,* a nitrite salt, such as $NaNO_2$). Hence, in one aspect, there is provided a process for making zilpaterol or a salt thereof, wherein the process comprises: making 4,5-dihydro-imidazo[4,5,1-jk][1]benzazepin-2,6,7[1H]-trione-6-oxime (or a salt thereof) by a process comprising reacting 8,9-dihydro-2H,7H-2,9a-diazabenzo[cd]azulene-1,6-dione (or a salt thereof) with an inorganic nitrite.

[14] This disclosure also is directed, in part, to a process for making chloro 2,3-dihydro-2-oxo-1H-benzimidazol-1-butanoate or a salt thereof. This process comprises reacting 4-(2-oxo-2,3-dihydrobenzimidazol-l-yl)butyric acid (or a salt thereof) with at least one chlorinating agent, such as oxalyl chloride, phosgene, and/or triphosgene.

[15] This disclosure also is directed, in part, to a process for making 8,9-dihydro-2H,7H-2,9a-diazabenzo[cd]azulene-l,6-dione or a salt thereof. This process comprises making chloro 2,3-dihydro-2-oxo-lH-benzimidazol-1 -butanoate (or a salt thereof) by a process comprising reacting 4-(2-oxo-2,3-dihydrobenzimidazol-l-yl)butyric acid (or a salt thereof) with at least one chlorinating agent, such as oxalyl chloride, phosgene, or triphosgene. In addition, the process comprises reacting chloro 2,3-dihydro-2-oxo-1H-benzimidazol-1 -butanoate (or a salt thereof) with a Lewis acid *(e.g.,* $AlCl_3$).

[16] In another aspect, there is provided a process for making 4,5-dihydro-imidazo[4,5,1-jk][1]benzazepin-2,6,7[1H]-trione-6-oxime or a salt thereof, wherein the process comprises reacting 8,9-dihydro-2H,7H-2,9a-diazabenzo[cd]azulene-1,6-dione (or a salt thereof) with an inorganic nitrite.

[17] This disclosure also is directed, in part, to a method of feeding an animal. This method comprises feeding to an animal *(e.g.,* a bovine animal, a swine animal, or a bird) zilpaterol or a salt thereof made by a process of this disclosure. Such feeding methods may be used, for example, to increase the animal's rate of weight gain, improve the animal's feed efficiency, and/or increase the animal's carcass leanness.

[18] This disclosure also is directed, in part, to a use of zilpaterol or a salt thereof, made by a process of this disclosure, to make a medicament. Uses for such a medicament include increasing an animal's rate of weight gain, improving an animal's feed efficiency, and/or increasing an animal's carcass leanness.

[19] Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this specification.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[20] This detailed description of preferred embodiments is intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This

4. A process for making 4,5-dihydro-imidazo[4,5,1-jk][1]benzazepin-2,6,7[1H]-trione-6-oxime or a salt thereof, wherein the process comprises reacting 8,9-dihydro-2H,7H-2,9a-diazabenzo[cd]azulene-1,6-dione (or a salt thereof) with an inorganic nitrite.

5. The process according to any one of claims 1 to 4, wherein the inorganic nitrite comprises a nitrite salt.

6. The process according to claim 5, wherein the nitrite salt comprises $NaNO_2$.