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6-HALOGEN-3-HYDROXY-BENZOATES AND PROCESS OF PREPARING THEM

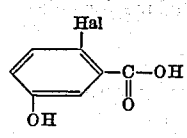
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6 Claims. (Cl. 260—473)

The present invention relates to compounds which are suitable as anthelminthics and which correspond to the general formula



wherein Hal represents chlorine, bromine or iodine and R an alkyl radical with 4 to 5 carbon atoms, and to the process for the manufacture of such compounds.

A great number of compounds belonging to entirely different classes have already been employed for the chemotherapy of helminthiases in human beings and animals. Apart from different drugs such as ascaridol and santonin there have also been recommended chlorinated hydrocarbons such as tetrachloroethylene, substituted phenols and their derivatives, such as para-chlorocarvacrol, para-bromothymol, hexylresorcinol, para-tertiary-amyl-phenol propionate. Other compounds, for instance dystuffs, such as crystal violet and different heterocyclic compounds, such as phenothiazine, do not come into consideration owing to their different constitution. In practice, however, it has been found that the known compounds partly only possess specific action on certain kinds of intestinal worms and that the therapeutic range of all these compounds is relatively small so that, even when the therapeutic dose is only little exceeded, disagreeable symptoms result.

Now we have found that 6-halogen-3-hydroxy-benzoates are obtained, which, apart from a satisfactory action on the parasites, possess at the same time a high therapeutic index and a broad therapeutic range, by esterifying 6-halogen-3-hydroxy-benzoic acids according to known methods with alcohols containing a linear or branched aliphatic chain with 4 to 5 carbon atoms. These 6-halogen-3-hydroxy-benzoates can also be prepared by reesterification.

As esterification components there may, for instance, be used n-butanol, isobutanol and isoamyl alcohol.

As halogen substituents in the benzene nucleus there are suited chlorine, bromine and iodine.

The reaction of the process of the present invention can, for instance, be carried out according to the following methods:

(*a*) By direct esterification in the presence of catalytically effective substances, for instance, in the presence of gaseous hydrogen halides, concentrated sulphuric acid or concentrated phosphoric acid.

(*b*) By reesterification which can be carried out in the usual manner, for instance, in the presence of an alcoholate as catalyst.

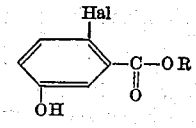
Naturally, there may also be employed other methods known for the preparation of esters.

According to the invention, the reaction may also be

carried out in the presence or absence of a diluent. As such may advantageously be used an excess of the alcohol required for the esterification. The reaction may be carried out at room temperature as well as at elevated temperatures, the reaction at elevated temperatures being terminated in lesser time.

The compounds obtained according to the process of the present invention are valuable medicaments and are particularly suited as anthelminthics. Apart from a very good tolerability they possess a marked efficacy.

It is remarkable that, in spite of the presence of a free phenolic hydroxy group, the therapeutic range of the compounds obtained according to the process of the present invention is considerably superior to that of the anthelminthics used at present. This is surprising since the small therapeutic range of various known anthelminthics on the basis of phenols is attributed to the presence of free phenolic hydroxy groups. We have found that the good tolerability is only shown by the benzoates which have the following special constitution:



wherein Hal and R have the meanings given above. It was found that the esters of other halogenated hydroxybenzoic acids, for instance, esters of 4-chloro-2-hydroxybenzoic acid or of 5-chloro-2-hydroxy-benzoic acid show, at a relatively low tolerability, also a low efficacy and sometimes none at all. The known benzoates whose phenyl radical is either substituted by halogens or by alkoxy groups, for instance, the 2.4-dichloro-benzoic acid isoamyl ester, or the polyphenol carboxylic acid esters have likewise proved to be unsatisfactory as regards their tolerability and also their efficacy.

Whilst the therapeutic index hereinafter defined amounts to 5.0–6.5 for ascaridol, to 5.0–6.0 for hexyl resorcinol, and to 5.0–6.0 for para-bromothymol, a considerably higher index is found for the compounds of the present invention. 6-chloro-3-hydroxy-n-butyl-benzoate, for instance, has a therapeutic index of 12–14. The therapeutic index is the quotient from the minimum toxic dose per kg. determined per os in the mouse and from the curative dose per kg. determined in the dog. The data result from tests on the ankylostomiasis and ascaridiasis of the dog. The known 2.4-dichloro-isoamyl benzoate did not show any effect on the dog suffering from ascaridiasis when applied in a dose nearly twice as large as the curative dose of the 6-chloro-3-hydroxy-n-butyl-benzoate.

The pharmacological data of some compounds obtained according to the process of the present invention and their therapeutic indices, which are superior to those of the known 6-chloro-3-hydroxy-ethyl benzoate (No. 5), are to be seen from the following table:

No.	Compound	Cur. dose per kg. of dog	Min. toxic dose per kg. of mouse	Therapeutic index
1	6-Chloro-3-hydroxy-iso-amyl benzoate.	0.3 cc.	7.0 cc.	23
2	6-Chloro-3-hydroxy-n-butyl benzoate.	0.4–0.5 gm.	5.0 gm.	10–12
3	6-Chloro-3-hydroxy-iso-butyl benzoate.	0.4 cc.	7.0 cc.	17
4	6-Bromo-3-hydroxy-n-butyl benzoate.	0.3–0.4 cc.	5.0 cc.	12–14
5	6-Chloro-3-hydroxy ethyl benzoate.	0.5–0.6 gm.	3.6 gm.	6–7

The following examples serve to illustrate the invention, but they are not intended to limit it thereto:

EXAMPLE 1

6-chloro-3-hydroxy-n-butyl-benzoate

Gaseous hydrogen chloride is introduced within 5 hours into the boiling solution of 344 grams of 6-chloro-3-hydroxy-benzoic acid in 800 grams of n-butanol and the whole is then boiled for about 12 hours. The butanol in excess is distilled off as completely as possible under reduced pressure, the residue is taken up in ether and the ethereal solution is shaken twice with a sodium bicarbonate solution. The ether is distilled off and the remaining residue is fractionated under reduced pressure. The 6-chloro-3-hydroxy-n-butyl benzoate passes over in an analytically pure form at 203–204° C. under a pressure of 11–12 mm. of mercury as a yellowish oil which soon solidifies in the receiving vessel. The yield amounts to 390 grams (85 percent of the theoretical yield). The white crystals obtained upon recrystallisation from cyclohexane melt at 42–43° C.

EXAMPLE 2

6-chloro-3-hydroxy-isoamyl-benzoate

Gaseous hydrogen chloride is introduced within 7 hours into the solution of 86 grams of 6-chloro-3-hydroxy-benzoic acid in 250 grams of isoamyl alcohol heated to about 100° C. The whole is then heated for another 7 hours at 100° C. and is worked up as described in Example 1. The 6-chloro-3-hydroxy-isoamyl-benzoate is obtained in the form of a non-crystalline, weakly yellowish oil boiling at 173–176° C. under a pressure of 1–2 mm. of mercury. The yield amounts to 100 grams (82 percent of the theoretical yield).

EXAMPLE 3

6-chloro-3-hydroxy-isobutyl-benzoate

A mixture of 120 grams of 6-chloro-3-hydroxy-benzoic acid, 160 grams of isobutanol and 30 grams of concentrated sulfuric acid is boiled for 15 hours under reflux. Thereupon ether is added and the mixture is shaken several times and successively with water, with a sodium bicarbonate solution and again with water. After drying and distilling off the solvent, a residue remains which is fractionated twice under reduced pressure. The 6-chloro-3-hydroxy-isobutyl-benzoate passes over as a yellowish oil at 153–154° under a pressure of 1–2 mm. of mercury. The yield amounts to 100 grams (70 percent of the theoretical yield).

EXAMPLE 4

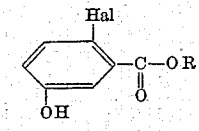
6-bromo-3-hydroxy-n-butyl-benzoate

Gaseous hydrogen chloride is introduced within 6 hours into the boiling solution of 100 grams of 6-bromo-3-hydroxy-benzoic acid in 240 grams of n-butanol and the whole is then boiled for another 6 hours. The butanol in excess is evaporated as completely as possible under reduced pressure, the residue is taken up in ether and the ethereal solution is shaken repeatedly with a sodium bicarbonate solution. The ether is distilled off and the

residue that remains is fractionated three times under reduced pressure. The 6 - bromo - 3 - hydroxy-n-butyl-benzoate distils over as a yellowish oil at 172–176° C. under a pressure of 0.9–1.2 mm. of mercury. The yield amounts to 78 grams (62 percent of the theoretical yield).

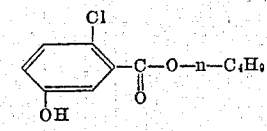
We claim:

1. 6-halogen-3-hydroxy-benzoates of the general formula

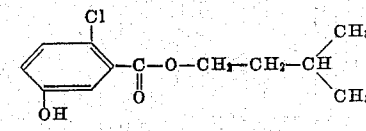


wherein Hal is a member selected from the group consisting of chlorine, and bromine and R represents an alkyl radical containing 4 to 5 carbon atoms.

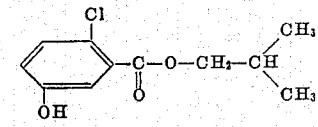
2. The compound of the formula



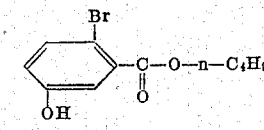
3. The compound of the formula



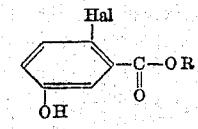
4. The compound of the formula



5. The compound of the formula



6. The process of preparing 6-halogen-3-hydroxy-benzoates of the general formula



wherein Hal is a member selected from the group consisting of chlorine, and bromine and R represents an alkyl radical containing 4 to 5 carbon atoms, which comprises esterifying 6-halogen-3-hydroxy-benzoates with aliphatic alcohols containing 4–5 carbon atoms.

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