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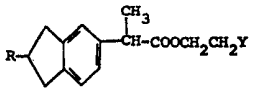
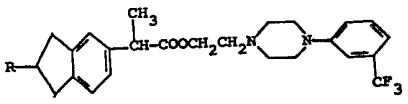
(54) Indane Acetic Acid Haloesters

(57) Novel compounds of formula:



when R is ethyl or isopropyl and Y is a halogen atom, which are useful as starting materials to manufacture the analgesics of formula



Claimed in Application No. 7923195 [Serial No. 2027019], may be prepared by esterification.

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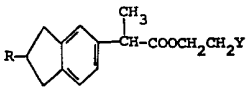
SPECIFICATION

Indane Acetic Acid Haloesters

This invention provides some novel indane acetic acid esters, and the method of making them. The esters of this invention can be used as starting materials for the preparation of indane amino esters which are valuable as analgesics.

The pharmaceutical properties of the indane amino esters which can be made from the esters of the present invention are described in our co-pending Application No. 7923195, (Serial No. 2027019). That application describes also the preparation of the analgesic amino esters by a route in which the indane esters of the present invention are formed as intermediates.

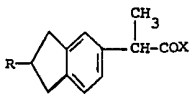
The indane acetic acid esters of the present invention have the formula



(I)

where R is ethyl or isopropyl and Y is a halogen atom.

They can be made by reacting the corresponding indane acyl halide of the formula



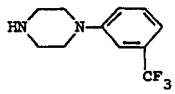
(II)

(where X is a halogen atom, not necessarily the same as Y, and R is ethyl or isopropyl) with a halo-alcohol of the formula

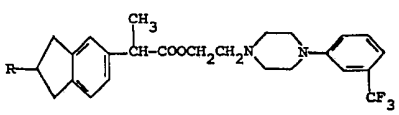
$$HO—CH_2CH_2—Y$$

(where Y is a halogen atom).

According to the invention the halogeno ester of formula (I) can be reacted with an m-trifluoromethylphenylpiperazine of formula (III)



in an organic solvent as acetone, chloroform, methylene chloride or an aromatic hydrocarbon using either a stoichiometric excess of the piperazine of formula III or a tertiary nitrogen-containing base such as triethylamine, to obtain a compound of formula (IV)



The compounds of formula (IV) are analgesics and are claimed *per se* in our co-pending Application No. 7923195.

The invention will now be illustrated by Examples.

Example 1

Preparation of starting materials

(a) 2-Methyl-(2-ethylindan-5-yl)-acetic acid chloride.

A solution of 57 g of 2-methyl-(2ethylindan-5-yl)-acetic acid and 40 ml of thionyl chloride in 200 ml of benzene is heated under reflux for 2 hours. The solvent and the excess thionyl chloride are then evaporated off *in vacuo.* The resulting oil is then distilled *in vacuo*. 56 g of 2-methyl-(2-ethylindan-5-yl)-acetic acid chloride are thus recovered in the form of a liquid:

Boiling point (1 mm Hg)=125—128°C.

(b) 2-Methyl-(2-isopropylindan-5-yl)-acetic acid chloride.

By following the procedure of (a), but using 31 g of 2-methyl-(2-isopropylindan-5-yl)-acetic acid, 30 g of 2-methyl-(2-isopropylindan-5-yl)-acetic acid chloride are recovered in the form of a liquid:

Boiling point (1mm Hg)=150°C.

Example 2

2-Methyl-(2-ethylindan-5-yl)-acetic acid bromoethyl ester.

Formula (I) R=ethyl Y=Br.

A solution of 4.4 g of 2-methyl-(2-ethylindan-5-yl)-acetic acid chloride and 2.45 g of 2-bromoethanol in 50 ml of anhydrous acetone is heated under reflux for 4 hours.

After evaporating off the solvent, the resulting oily residue is dissolved in ether and the ether solution is washed, in the presence of ice, with an aqueous solution of sodium bicarbonate and with water and is then dried over sodium sulphate. After filtering and evaporating off the solvent, 5.9 g of 2-methyl-(2-ethylindan-5-yl)-acetic acid bromoethyl ester are obtained in the form of an oil residue which is used in the crude state for the following step (Example 4).

Example 3

Same product as Example 2

A solution of 12 g of 2-methyl-(2-ethylindan-5-yl)-acetic acid chloride in 15 ml of chloroform is added, at 0°C to a solution of 6.4 g of 2-bromoethanol and 5.5 ml of pyridine in 30 ml of chloroform.

After the addition is complete, the reaction mixture is heated under reflux for 1 hour.

After cooling, the reaction mixture is washed with water, with 5% strength hydrochloric acid and then again with water. The chloroform phase is dried and, after evaporating off the solvent, the oily residue is distilled *in vacuo.* 13.7 g of 2-methyl-(2-ethylindan-5-yl)-acetic acid bromoethyl ester are thus recovered in the form of an oil.

Boiling point (0.2 mm Hg)=138—148°C.

Example 4
Use of product of Example 2 in preparation of an analgesic
2-Methyl-(2-ethylindan-5-yl)-acetic acid m-trifluoro-methylphenylpiperazinoethyl ester hydrochloride.

Formula (IV), R=ethyl.

A solution of 5.9 g of 2-methyl-(2-ethylindan-5-yl)-acetic acid bromoethyl ester obtained by Example 2, in 15 ml of anhydrous acetone, is added to a solution of 4.2 g of m-trifluoromethylphenylpiperazine and 3 ml of triethylamine in 25 ml of anhydrous acetone.

The reaction mixture is stirred for 2 hours at ambient temperature and then heated under reflux for 6 hours.

After cooling, the triethylamine hydrobromide formed is filtered off and the filtrate is concentrated *in vacuo.*

The resulting residue is taken up in ether and the mixture is again filtered.

The new filtrate recovered is concentrated *in vacuo.* 9.8 g of oil are thus obtained.

This oil is dissolved in 50 ml of acetone, 25 ml of water are then added and the mixture is acidified to pH 3 with concentrated hydrochloric acid.

The crystals formed are filtered off, washed with water and then with acetone and dried.

2.7 g of 2-methyl-(2-ethylindan-5-yl)-acetic acid m-trifluoromethylphenylpiperazinoethyl ester hydrochloride are thus recovered in the form of white crystals having a melting point of 201—203°C.

Example 5
Use of product of Example 3 in preparation of an analgesic

A solution of 13.6 g of the 2-methyl-(2-ethylindan-5-yl)-acetic acid bromoethyl ester prepared in Example 3, 9.6 g of m-trifluoromethylphenylpiperazine, 7 ml of triethylamine and 200 mg of sodium iodide, in 100 ml of anhydrous benzene, is heated under reflux for 10 hours.

The reaction mixture is cooled, washed carefully with water and dried over sodium sulphate and the benzene is evaporated off *in vacuo.*

The resulting oily residue, weighing 20 g, is taken up in 60 ml of acetone, and 3.5 ml of concentrated hydrochloric acid, and then 40 ml of water, are added in the cold.

The crystals formed are filtered off, washed with a small amount of water and then with acetone and dried.

14.2 g of 2-methyl-(2-ethylindan-5-yl)-acetic acid m-trifluoromethylphenylpiperazinoethyl ester hydro-chloride are thus recovered in the form of white crystals having a melting point of 202—203°C.

Example 6
2-Methyl-(2-isopropylindan-5-yl)-acetic acid bromoethyl ester

Formula I, R=isopropyl Y=Br.

A solution of 32 g of 2-methyl-(2-isopropyl-indan-5-yl)-acetic acid chloride in 25 ml of chloroform is added, at 0°C, to a solution of 16 g of 2-bromoethanol and 14 ml of pyridine in 50 ml of chloroform.

After the addition is complete, the reaction mixture is heated under reflux for 1 hour.

After cooling, the reaction mixture is washed with water, with 5% strength hydrochloric acid and then again with water.

The chloroform phase is dried and, after evaporating off the solvent, the oily residue, weighing 49 g, is distilled *in vacuo.* 35.2 g of 2-methyl-(2-isopropylindan-5-yl)-acetic acid bromoethyl ester are thus recovered in the form of an oil.

Boiling point (1.5 mm Hg)=165—175°C.

Example 7
Same product as Example 6

A solution of 32 g of 2-methyl-(2-isopropylindan-5-yl)-acetic acid chloride in 25 ml of acetone is added dropwise to a solution of 16 g of 2-bromoethanol and 10.4 ml of pyridine in 125 ml of acetone.

After the addition is complete, the reaction mixture is heated under reflux for 1 hour 30 minutes.

The reaction mixture is then concentrated *in vacuo*, the residue is taken up in ether and the resulting mixture is washed with water, with 5% strength hydrochloric acid and then again with water. The ether phase is dried and the solvent is evaporated off *in vacuo.*

40 g of 2-methyl-(2-isopropylindan-5-yl)-acetic acid bromoethyl ester are thus recovered in the form of an oil which is used in the crude state for the following operations (Example 9).

Example 8
Use of product of Example 6 in preparation of an analgesic
2-Methyl(2-isopropylindan-5-yl)-acetic acid m-trifluoro-methylphenylpiperazinoethyl ester hydrochloride.

Formula IV, R=isopropyl.

A solution of 35.2 g of the 2-methyl-(2)isopropylindan-5-yl)-acetic acid bromoethyl ester prepared in Example 6, 47.8 g of m-trifluoromethyl-phenylpiperazine and 1 g of sodium iodide, in 300 ml of anhydrous toluene, is heated under reflux for 8 hours.

The reaction mixture is cooled and the m-trifluoromethylphenylpiperazine hydrobromide is filtered off and washed with benzene.

The organic filtrate is washed with water and then dried and concentrated *in vacuo.*

The resulting oily residue, weighing 61.7 g, is taken up 250 ml of acetone, and 8.7 ml of concentrated hydrochloric acid, and then 150 ml of water, are added in the cold.

The resulting crystals are filtered off, washed with a small amount of water and then acetone and dried.

35.7 g of 2-methyl-(2-isopropylindan-5-yl)-acetic acid m-trifluoromethylphenylpiperazinoethyl ester hydrochloride are thus recovered in the form of white crystals having a melting point of 191—193°C.

Example 9

Use of product of Example 7 in preparation of an analgesic.

A solution of 40 g of the 2-methyl-(2-isopropylindan-5-yl)-acetic acid bromoethyl ester prepared in Example 7, 31.5 g of m-trifluoromethylphenylpiperazine hydrochloride and 36.5 ml of triethylamine, in 200 ml of acetone, is heated under reflux for 8 hours.

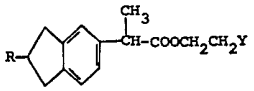
The reaction mixture is then concentrated *in vacuo*, the residue is taken up in a mixture of water and ice and the resulting mixture is extracted with ether. The ether phase is washed with water, dried over sodium sulphate and then concentrated *in vacuo*.

The resulting residue, weighing 57 g, is taken up in 150 ml of acetone, and 10 ml of concentrated hydrochloric acid, and then 100 ml of water, are added. The crystals formed are filtered off, washed with a small amount of water and then acetone and dried.

27.4 g of 2-methyl-(2-isopropylindan-5-yl)-acetic acid m-trifluoromethylphenylpiperazinoethyl ester hydrochloride are thus recovered in the form of white crystals having a melting point of 193—194°C.

Claims

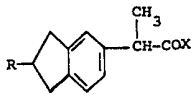
1. An indane acetic acid ester having the formula:



where R is ethyl or isopropyl and Y is a halogen atom.

2. An ester according to claim 1 where Y is bromine or chlorine.

3. Method of preparing a compound according to claim 1 which comprises reacting an indane acyl halide of formula



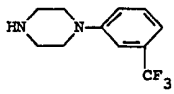
where X is a halogen atom, with a haloalcohol of formula HO—CH_2—CH_2—Y where R is ethyl or isopropyl and Y is a halogen atom.

4. Method according to claim 3 when Y is chlorine or bromine.

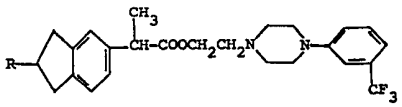
5. Method of preparing a compound according to claim 1 substantially as described in Example 2, 3, 6 or 7 herein.

6. A compound according to claim 1 when prepared by a method according to claim 3, 4 or 5.

7. Use of a compound according to claim 1, 2 or 6 as starting material for reaction with a piperazine of formula:



to prepare a compound of formula:



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