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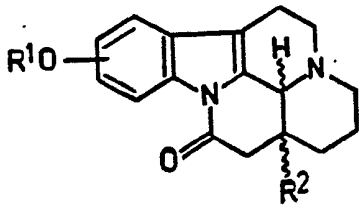
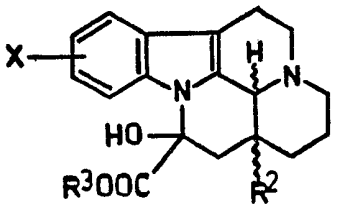
(54) **Alkoxyvincamone derivatives**

(57) A process for the preparation of alkoxyvincamone derivatives of the formula (I)



I

(wherein R^1 and R^2, which may be the same or different, each represents an alkyl group having from 1 to 6 carbon atoms) comprising reacting a halovincaminic acid ester of the formula (II)



(II)

(wherein R^2 is as defined above R^3 represents an alkyl group having from 1 to 6 carbon atoms, and X represents a halogen atom) with an alkali metal alkanoate of the formula R^1–OMe, (wherein R^1 is as defined above and Me represents an alkali metal atom), in the presence of a catalyst. Compounds of formula I other than (−)-vincinone are also claimed.

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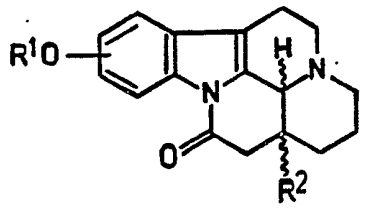
SPECIFICATION

Alkoxyvincamone derivatives

The invention relates to a new process for the preparation of alkoxyvincamone derivatives of the formula (I)



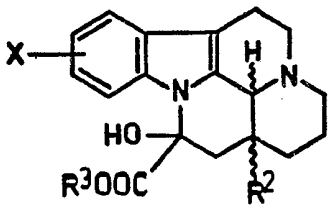
(I)

(wherein R^1 and R^2, which may be the same or different, each represents an alkyl group having from 1 to 6 carbon atoms).

The compounds of formula (I) are pharmaceutically active as well as being useful starting materials in the preparation of other pharmaceutically active compounds having an eburnane skeleton. These compounds are new compounds except for (−)-vincinone, i.e. a compound of the formula (I), in which R^2 is an α-ethyl group, R^1 is methyl, the R^1O group is attached to the 11-position of the eburnane skeleton and the hydrogen is in α-position which is known. Thus (−)-vincinone occurs naturally in Vinca minor [Tetrahedron Letters *15*, 1805–1806 (1968)] and can be prepared synthetically by nitrating (−)-vincamone (yield: 77%), reducing the 11-nitro-vincamone obtained (yield: 80%), diazoting the 11-amino-vincamone obtained, converting the formed diazonium salt into 11-hydroxy-vincamone directly, without isolation, in a known manner (yield: 50%) and finally reacting the 11-hydroxy-vincamone produced with diazomethane to produce (−)-vincinone (yield: 30%). However the total yield of the five subsequent reaction steps is only 9.2% [see Bull. Soc. Chim. Belg. *88*. 93 (1979)].

We have now surprisingly found that by reacting halovincaminic acid esters with alkali metal alkanoates of the formula R^1–OMe containing the desired R^1O moiety in the presence of a suitable catalyst, not only (−)-vincinone but also the other alkoxyvincamone derivatives of formula (I), may be obtained in a single reaction step, with a 66% yield.

Thus according to the present invention we provide a process for the preparation of alkoxyvincamone derivatives of the formula (I) as hereinbefore defined which comprises reacting a halovincaminic acid ester of the formula (II)



(II)

(wherein R^2 is as defined above, R^3 represents an alkyl group having from 1 to 6 carbon atoms and X represents a halogen atom) with an alkali metal alkanoate of the formula R^1–OMe, (wherein R^1 is as defined above and Me represents an alkali metal atom), in the presence of a catalyst.

In the definition of R^1, R^2 and R^3 the term "alkyl having from 1 to 6 carbon atoms" is used to refer to straight or branched chained alkyl groups having from one to 6 carbon atoms, e.g. methyl, ethyl, *n*-propyl, iso-propyl, *n*-butyl, sec-butyl, tert-butyl, *n*-pentyl, iso-pentyl, *n*-hexyl or isohexyl, preferably methyl or ethyl. X may represent fluorine, chlorine, bromine or iodine, preferably bromine.

In the formula (I) the group R^1O may be attached to the benzene ring in any position and the actual site of attachment depends on the position of X in the starting materials of the formula (II). The 9-, 10- and 11-alkoxy-vincamones are preferred.

The starting compounds of the formula (II) can for example be prepared as described in Hungarian Patent Application RI-675 and Hungarian Patent Specification 178 702.

As a catalyst in the reaction of the compounds of formula (II) with alkali metal alkanoates of the formula R^1–OMe for example an inorganic salt containing a monovalent copper ion can be employed. Such catalysts include, for example, cuprous iodide, cuprous rhodanide, cuprous chloride and cuprous bromide, cuprous bromide being preferred.

As a solvent for example alkanols of the formula R^1–OH, corresponding to the R^1–OMe reactant and dimethylformamide, dimethylacetamide, 2,4,6-collidine, 2,6-lutidine or pyridine,

preferably dimethylformamide are employed. The reaction is preferably carried out at a temperature of from 25°C to 140°C.

Relative to the starting compounds of the formula (II) preferably 3 to 15 equivalents of the alkanoate of formula R^1–OMe and 0.5 to 4 equivalents of cuprous salt are used.

Further details of the invention are illustrated by the following example which is for illustration and not for limitation of our invention.

Example

(−)-Vincanone [(−)-11-methoxy-vincamone]

0.12 g. (5.21 mmoles) of sodium metal are dissolved in 1.6 ml. of absolute methanol, under nitrogen. To the solution 2.5 ml. of absolute dimethylformamide and 0.25 g. (1.31 mmoles) of cuprous iodide are added followed by the addition of 0.20 g. (0.46 mmoles) of (+)-11-bromo-vincamine (Hungarian Patent Specification 178 702). The reaction mixture is allowed to stand at 110°C for 1.5 hours, with continuous stirring. Upon cooling the mixture is poured onto 7 ml. of ice water, shaken with 5 ml. of ethyl acetate and the inorganic precipitate is filtered off. The organic phase is separated from the filtrate and the aqueous phase is extracted with three 5-ml. portions of ethyl acetate. The combined ethyl acetate phases are shaken with two 3-ml. portions of water, the organic layer is dried with solid, anhydrous magnesium sulfate, filtered and from the filtrate the solvent is eliminated in *vacuo*. The residual oil is crystallized from 1 ml. of methanol. 0.10 g. (66%) of the title compound are obtained.

Melting point: 168 to 170°C (methanol)

(Literature melting point data: 161 to 162°C (acetone)
—Bull. Soc. Chim. Belg. *88*, 93 (1979);
168 to 169°C
—Tetrahedron Letters, 1968, 1805;
169 to 170°C
Collect. Czech. Chem. Commun. *29*, 447, 1964).

IR (KBr): 1700 (lactame CO); 1620 cm^{-1} (aromatic)

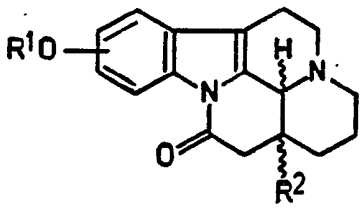
Mass spectrum m/e (%): 324 (M^+, $C_{20}H_{24}N_2O_2$, 100); 323 (80); 296 (12); 295 (26); 294 (8.8); 293 (8.3); 267 (18); 254 (20); 252 (8.3); 197 (9.4).

$[\alpha]_D = -112.2°$; $[\alpha]_{546} = -137.7°$ (c = 0.70; chloroform).

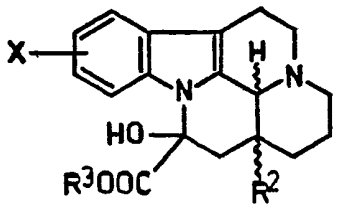
(Literature data: $[\alpha]_D = -107°$ (c = 0.37; chloroform)—Bull. Soc. Chim. Belg. *88*, 93, 1979); −118° (Tetrahedron Letters, *1968*, 1805].

CLAIMS

1. A process for the preparation of alkoxyvincamone derivatives of the formula (I)



(wherein R^1 and R^2, which may be the same or different, each represents an alkyl group having from 1 to 6 carbon atoms) which comprises reacting a halovincaminic acid ester of the formula (II)



(wherein R^2 is as defined above, R^3 represents an alkyl group having from 1 to 6 carbon atoms and X represents a halogen atom) with an alkali metal alkanoate of the formula R^1–OMe, (wherein R^1 is as defined above and Me represents an alkali metal atom), in the presence of a catalyst.

2. A process as claimed in claim 1 wherein the catalyst is a cuprous salt.

3. A process as claimed in claim 2 wherein the catalyst is cuprous iodide, cuprous rhodanide, cuprous chloride or cuprous bromide.

4. A process claimed in any preceding claim wherein the reaction is effected in the presence

of a solvent.

5. A process as claimed in claim 4 wherein the solvent comprises an alkanol of formula R^1OH (wherein R^1 is as defined in claim 1) and dimethylformamide, dimethylacetamide, 2,4,6-collidine, 2,4-lutidine or pyridine.

6. A process as claimed in any preceding claim wherein X in the compound of formula (II) is in the 9-, 10- or 11-position.

7. A process as claimed in any preceding claim wherein X represents a bromine atom.

8. A process for preparation of compounds of general formula I as claimed in claim 1 substantially as herein described.

9. A process for preparation of compounds of general formula I as defined in claim 1 substantially as herein described in the Example.

10. Compounds of general formula I as defined in claim 1 whenever prepared by a process as claimed in any one of claims 1 to 9.

11. Compounds of general formula I as defined in claim 1 other than (−)-vincinone.

12. Each and every novel method, process, compound and composition herein disclosed.

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