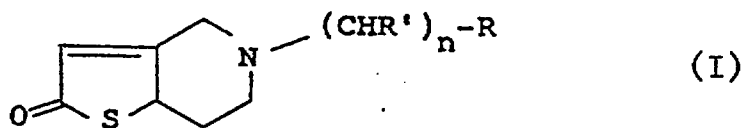


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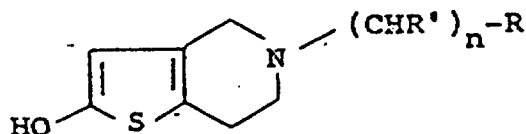
Novel process for the preparation of 5,6,7,7a-tetrahydro-4H-thieno(3,2-c)pyridin-2-ones

The present invention relates to a novel process for the preparation of 5,6,7,7a-tetrahydro-4H-thieno-(3,2-c)pyridin-2-one derivatives of formula:



in which R represents hydrogen or a phenyl radical optionally substituted by at least one halogen atom, lower alkyl radical, lower alkoxy radical, nitro group, carboxy group, alkoxycarbonyl radical or cyano group; R' represents hydrogen or a lower alkyl radical and n is zero or an integer between 1 and 4; as well as the addition salts thereof with mineral and organic acids.

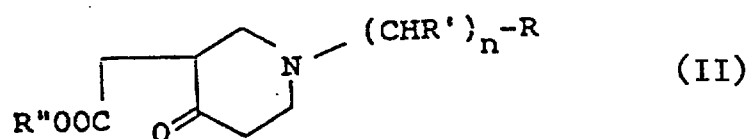
These compounds have platelet anti-aggregant properties and anti-thrombotic properties form the subject matter of the patent application EP-A-005442 filed by the Applicant. They are also included in a general formula claimed in French patents 2,215,948 and 2,345,150 in their following tautomeric form:-



However, none of these products is specifically described therein.

French patent application 2,338,703 discloses a process for the preparation of thieno-pyridine derivatives in which there is a two-stage cyclization of the thiophene cycle on the basis of a piperidone derivative, which is firstly condensed with a mercaptoacetic derivative and then cyclized with the aid of a base in an organic solvent.

The present invention relates to a process for the preparation of derivatives of the previously defined formula I, characterized in that a compound of the following formula:



in which R, R' and n have the same meanings as above and R'' is hydrogen or an alkyl radical containing 1 to 4 carbon atoms, is treated in an organic solvent with gaseous hydrogen chloride and gaseous hydrogen sulphide.

The action of the gaseous hydrogen chloride and of the gaseous hydrogen sulphide may occur simultaneously with a mixture of the two gases or by the separate and successive action of each of them.

The reaction is carried out in an organic solvent, such as a lower alkanol, for example methanol or ethanol, or a lower carboxylic acid, such as acetic acid or propionic acid, or in a mixture of these solvents. Working preferably takes place at a temperature between ambient temperature and the boiling point of the solvent used.

The keto acids and keto esters of general formula

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(II) were prepared by a process analogous to that described in published Japanese Patent Application Kokai No. 79 98 771 in the name of Tokyo Koho, which is abstracted in Chemical Abstracts, 92, 41773x/1980, for obtaining derivatives of general formula (II) in which $R'=H$, $R=C_6H_5$ and $n = 1$ or 2 .

The following examples illustrate the invention. The structure of the compounds obtained has been confirmed by microanalysis, infra-red spectroscopy and nuclear magnetic resonance.

Example 1

5-(2-chlorobenzyl)-5,6,7,7a-tetrahydro-4H-thieno-(3,2-c)-pyridin-2-one. (Formula I; $R = 2-Cl.C_6H_4$; $R=H$; $n = 1$).

a) Preparation of methyl [1-(2-chlorobenzyl)-4-oxo-3-piperidine]-acetate.

A solution of 100g (0.355 mole) of ethyl [1-(2-chlorobenzyl)-4-oxo-3-piperidine]-carboxylate (see J.P. Maffrand and D. Frehel, Bull. Soc. Chim. France, (1-2), II-48/1978) in 400 cc of 1,2-dimethoxyethane is added dropwise to a mixture of 17.04g (0.355 mole) of sodium hydride (50% suspension) in 250cc of 1,2-dimethoxyethane. The reaction mixture is stirred at ambient temperature for 30 minutes, after which a solution of 59.28g (0.355 mole) of ethyl bromoacetate in 250cc of 1,2-dimethoxyethane is added thereto dropwise.

The reaction mixture is stirred at ambient temperature for 2 hours and the precipitate formed is filtered off and washed with ether and the filtrate is concentrated in vacuo. The residue is taken up in water

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and extracted with methylene chloride. The organic extracts are washed with water, dried over sodium sulphate and filtered through a bed of silica and concentrated in vacuo.

The yellow resin obtained (123.2g) is dissolved in 850 cc of 6N hydrochloric acid and the solution is refluxed under nitrogen atmosphere for 4 hours. After cooling, the medium is concentrated in vacuo and water is added, followed by extraction with ether. The aqueous phases are rendered weakly basic by the addition of sodium carbonate, then adjusted to a pH of about 4 by the addition of acetic acid and extracted with methylene chloride. The organic phases are washed with water, dried with sodium sulphate and evaporated to dryness. The resinous product obtained (93.8g) is dissolved in acetone and treated with an ethereal solution of gaseous hydrogen chloride. The [1-(2-chlorobenzyl)-4-oxo-3-piperidine]-acetic acid hydrochloride obtained is filtered off, washed with acetone and then with ether and dried in vacuo. This compound is obtained in a yield of 64% in the form of white crystals; m.p. decomposes at about 180°C; IR (KBr) : $\nu_{\text{CO}} = 1728 \text{ cm}^{-1}$.

A solution of 30g of this hydrochloride in 300 cc methanol saturated with gaseous hydrogen chloride is stirred at ambient temperature for 3 hours. This is followed by evaporation in vacuo at a temperature below 50°C, the addition of water, made basic by the addition of sodium bicarbonate and extracted with methylene chloride. The organic extracts are washed with water, dried with

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sodium sulphate and evaporated to dryness. The yellow resin obtained is used, without further purification, for the following stage. IR (film): $\nu_{\text{CO}} = 1720 \text{ cm}^{-1}$; NMR (CDCl_3) = 7.05 - 7.65 (m, 4H); 3.72 (s, 2H); 3.62 (s, 3H).

b) 5-(2-chlorobenzyl)-5,6,7,7a-tetrahydro-4H-thieno-(3,2-c)-pyridin-2-one.

Currents of gaseous hydrogen chloride and of gaseous hydrogen sulphide are simultaneously bubbled into a solution, heated to 85°C ., of 4.5 g (0.0152 mole) of the keto ester obtained above in 45 cc of acetic acid. This is followed by concentration in vacuo taking up the residue in water, bringing to a basic pH by the addition of sodium bicarbonate and extraction with methylene chloride. The extracts are washed with water, dried with sodium sulphate and evaporated to dryness. The yellow oil obtained (3.6 g ; yield 86%) is converted into the oxalate by the addition of a solution of oxalic acid in acetone; m.p. 170°C (ethanol)

IR (KBr): $\nu_{\text{CO}} = 1660 \text{ cm}^{-1}$ (large).

The hydrochloride hemihydrate, after precipitation from acetone, decomposes at about 180°C .

The base melts at $73 - 74.5^\circ\text{C}$ (ethanol), NMR (CDCl_3) 7.1-7.6 (m, 4H); 6.2 (s, 1H); 4.2-4.7 (m, 1H); 3.9 (s, 2H); 1.5-4.2 (m, 6H).

Examples 2 to 9

The following compounds were prepared in the same manner.

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Derivative 2: 5-benzyl-5,6,7,7a-tetrahydro-4H-thieno-(3,2-c)-pyridin-2-one

formula (I) ($R = C_6H_5$; $R' = H$; $n = 1$)

maleate: beige crystals; m.p. 132-134°C

(isopropanol)

IR (KBr): $\sqrt{CO} : 1680 \text{ cm}^{-1}$

base: NMR ($CDCl_3$) : 7.25 (m, 5H); 5.90 (s, 1H); 3.60 (s, 2H).

Derivative 3: 5-(4-chlorobenzyl)-5,6,7,7a-tetrahydro-4H-thieno-(3,2-c)-pyridin-2-one

formula (I) ($R = 4\text{-Ch-C}_6\text{H}_4$; $R' = H$; $n = 1$)

maleate: beige crystals ; m.p. 158-160°C

(ethanol)

IR (KBr): $\sqrt{CO} = 1680 \text{ cm}^{-1}$

base: NMR ($CDCl_3$): 7.30 (m, 4H); 6.0 (s, 1H); 3.50 (s, 2H).

Derivative 4: 5-(2-methylbenzyl)-5,6,7,7a-tetrahydro-4H-thieno-(3,2-c)-pyridin-2-one

formula (I) ($R = 2\text{-CH}_3\text{-C}_6\text{H}_4$; $R' = H$; $n = 1$)

oxalate: beige crystals; m.p. 195-197°C

(methanol)

IR (KBr): $\sqrt{CO} = 1690 \text{ cm}^{-1}$

base: NMR ($CDCl_3$): 7.10 (s, 4H); 5.90 (s, 1H); 3.55 (s, 2H); 2.30 (s, 3H).

Derivative 5: 5-[1-(2-chlorophenyl)-ethyl]-5,6,7,7a-tetrahydro-4H-thieno-(3,2-c)-pyridin-2-one

formula (I) ($R = 2\text{-Cl-C}_6\text{H}_4$; $R' = CH_3$; $n = 1$)

hydrochloride: yellow crystals; m.p. 140-142°C.

IR (KBr): $\sqrt{CO} = 1690 \text{ cm}^{-1}$

base: NMR ($CDCl_3$): 7.30 (m, 4H); 6.05; 5.95 (2s, 1H); (2 diastereoisomers).

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Derivative 6: 5-[1-(2-chlorophenyl)-propyl]-5,6,7,7a-tetrahydro-4H-thieno(3,2-c)-pyridin-2-one

formula (I) ($R = 2\text{-Cl-C}_6\text{H}_4$; $R' = \text{C}_2\text{H}_5$; $n = 1$)

hydrochloride: beige crystals; m.p. 124-126°C.

IR (KBr): $\sqrt{\text{CO}} = 1690 \text{ cm}^{-1}$

base: NMR (CDCl_3): 7.30 (m, 4H); 6.05; 5.90 (2s, 1H)
(2 diastereoisomers).

Derivative 7: 5-(2-cyanobenzyl)-5,6,7,7a-tetrahydro-4H-thieno(3,2-c)-pyridin-2-one

formula (I) ($R = 2\text{-Cl-C}_6\text{H}_4$; $R' = \text{H}$; $n = 1$)

oxalate: beige crystals; m.p. 176-178°C.

(acetonitrile)

IR (KBr): $\sqrt{\text{CO}} = 1700 \text{ cm}^{-1}$; $\sqrt{\text{CN}} = 2210 \text{ cm}^{-1}$

base: NMR (CDCl_3): 7.50 (m, 4H); 6.00 (s, 1H); 3.80 (s, 2H).

Derivative 8: 5-(2-nitrobenzyl)-5,6,7,7a-tetrahydro-4H-thieno(3,2-c)-pyridin-2-one

formula (I) ($R = 2\text{-NO}_2\text{-C}_6\text{H}_4$; $R' = \text{H}$; $n = 1$)

oxalate: beige crystals; m.p. 186-188°C

(isopropanol-ethanol)

IR : $\sqrt{\text{CO}} = 1685 \text{ cm}^{-1}$

base: NMR (CDCl_3): 7.50 (m, 4H); 5.95 (s, 1H); 3.90 (s, 2H).

Derivative 9: 5-(2-bromobenzyl)-5,6,7,7a-tetrahydro-4H-thieno(3,2-c)-pyridin-2-one

formula (I) ($R = 2\text{-Br-C}_6\text{H}_4$; $R' = \text{H}$; $n = 1$)

oxalate: beige crystals; m.p. 151-153°C.

(isopropanol)

IR (KBr): $\sqrt{\text{CO}} = 1690 \text{ cm}^{-1}$

base: (CDCl_3): 7.30 (m, 4H); 5.95 (s, 1H); 3.75 (s, 2H).