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AN ALTERNATIVE SYNTHESIS OF CARDIOTONIC 6-(3,4-DIHYDRO-3-OXO-1,4(2H)BENZOXAZIN-7-YL)-2,3,4,5-TETRAHYDRO-5-METHYLPYRIDAZIN-3-ONES

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ABSTRACT : Useful therapeutic 6-(3,4-dihydro-3-oxo-1,4 (2H) benzoxazin-7-yl)-2,3,4,5-tetrahydro-5-methylpyridazin-3-ones can be conveniently prepared from 6-propionyl-1,3 benzoxazolin-2-ones using α, β unsaturated ketone as intermediate.

For the last few years, our laboratory was interested (Scheme 1) in the synthesis of 4-acyl and 5-acyl-2-amino phenols[1] (structures A and B) and their use in heterocyclisation reactions, particularly those leading to the 5-acyl-1,3 benzoxazolin-2-ones[2] (structure C) and the 7-acyl-3-oxo-1,4 (2H)benzoxazines[3,4] (structure D). We then used these latter compounds as starting materials and obtained a series of derivatives which showed significant normolipemic properties[5,6]. Knowing the numerous research efforts about the cardiotonic and vasodilatator activities of substituted-2,3,4,5-tetrahydro pyridazin-3-ones[7,8,9], we thought interesting to associate these two pharmacophoric patterns in the same structure and we therefore decided to prepare some 6-(3,4-dihydro-3-oxo-1,4 (2H) benzoxazin-7-yl)-2,3,4,5-tetrahydro-5-methylpyridazin-3-ones

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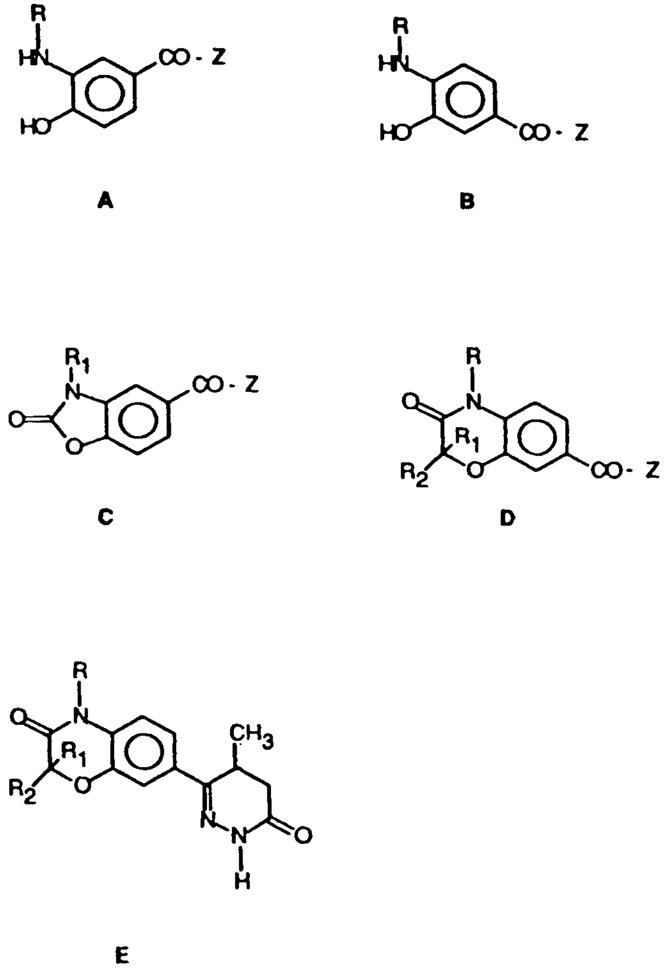


Scheme 1

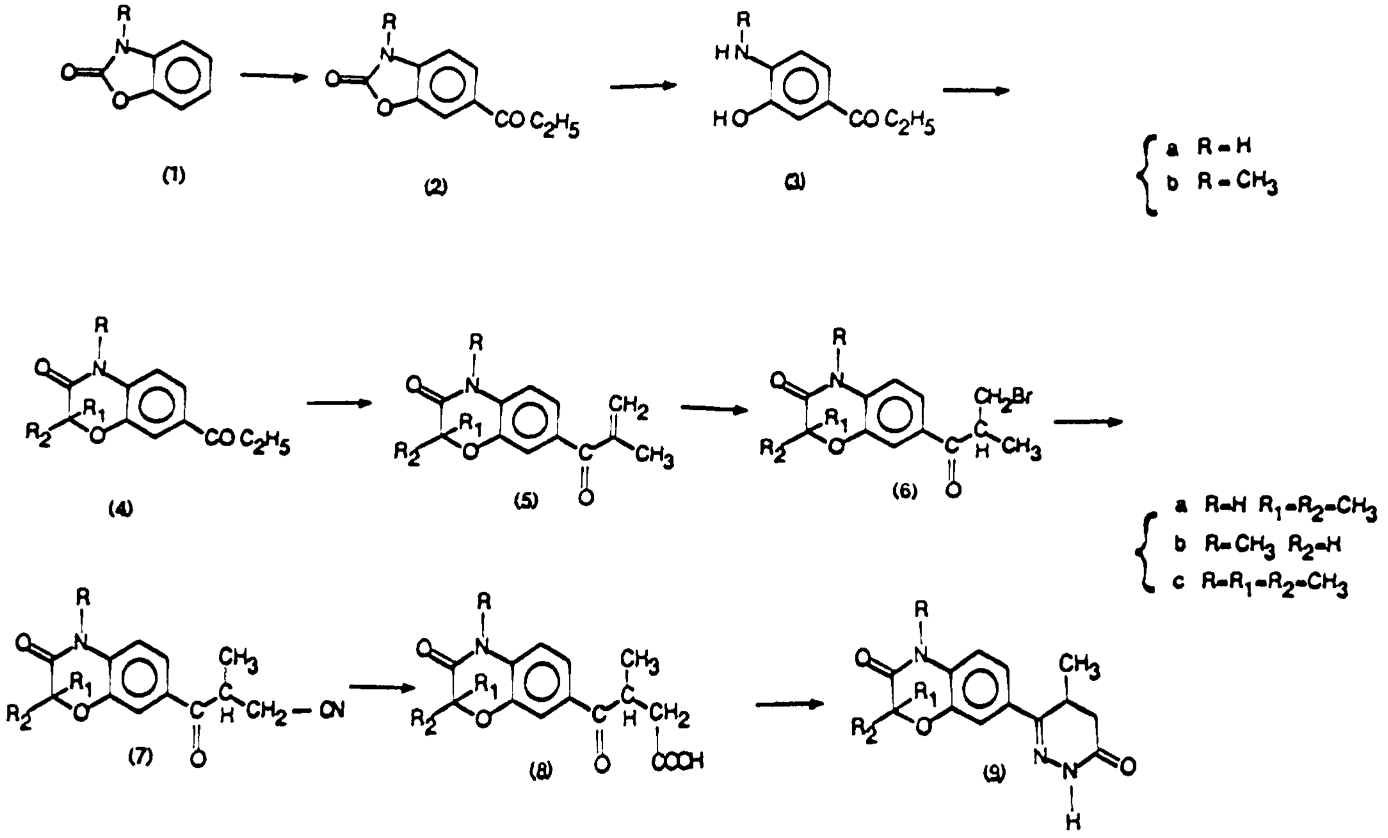
(structure E) from the corresponding 6-propionyl-1,3-benzoxazolin-2-ones. While these compounds were submitted to pharmacological studies, one reference[10] to some of them and their position isomers appeared. However, the published chemical ways were obviously different from ours and few physico-chemical data were reported for the intermediates and reaction products.

In this communication, it seems of interest to complete the knowledge about the tittle compounds and we report a convenient and flexible synthesis.

the synthesis of the 6-(3,4-dihydro-3-oxo-1,4 (2H)benzoxazin-7-yl)-5-methylpyridazin-3-ones (9 a-c) was achieved as shown in **scheme 2**. 1,3-benzoxazolin-2-ones (1 a-b) were treated with propanoic acid in polyphosphoric acid[11] and by alkaline hydrolysis[1] of the resulting 6-propionyl-1,3-benzoxazolin-2-ones (2 a-b) 5-propionyl-2-amino or (methylamino) phenols (3 a-b) were obtained. Reacting with an α halogeno carboxylic acid ester[3] they cyclised to 2,4-substitued-3,4-dihydro-3-oxo-7-propionyl-1,4 (2H)benzoxazines (4 a-c). Treatment of these ketones with N,N,N',N'-tetramethyldiamino methane[12] and acetic anhydrid led to α, β unsaturated ketones (5 a-c). HBr addition to the double bond, followed by reaction of the intermediary bromo compound (6 a-c) with potassium cyanide led to the nitriles (7 a-c). Hydrolysis by aqueous HCl gave the carboxylic acids (8 a-c) which were cyclised to the target molecules (9 a-c) by heating with hydrazine.

EXPERIMENTAL PART

Melting points were determined on a BUCHI 510 capillary apparatus and are uncorrected. Microanalyses were performed by CNRS laboratories (Vernaison). Infra-red spectra were obtained on a PERKIN-ELMER 297 spectrometer on KBr paths. ^{1}H.N.M.R spectra were obtained on a WP 80 BRUKER spectrometer. All NMR spectra were run in $CDCl_3$ unless otherwise specified. The spectra are reported relative to the internal standard tetramethylsilane as values in parts per million, using the following abbreviations : s, singulet ; d, doublet ; dd, doublet of doublet ; t, triplet ; q, quartet ; m, multiplet. For each compound, only the caracteristics resonances signals are mentionned comparatively to the key intermediate 4c whose spectrum can be described as follow (in ppm) : 1.2 (t,3H) ; 1.6 (d,3H) ; 2.5 (q,2H) ; 3.4 (s,3H) ; 5.6 (s,1H) ; 5.8 (s,1H) ; 7 (d,1H) ; 7.5 (d,1H) ; 7.6 (dd,1H). The starting materials 2 a-b and the intermediate (3-4 a,b,c) can be obtained from our previously described procedure[4,6].



Scheme 2

GENERAL PROCEDURE FOR THE SYNTHESIS OF 7-(2-METHYLENEPROPIONYL)-2,4 SUBSTITUTED-3,4-DIHYDRO-3-OXO-1,4(2H)BENZOXAZINES (5a-c)

To a stirred suspension of the ketone 4 (0.1mole) in N,N,N',N'-tetramethyl diaminomethane (50 ml) is added dropwise acetic anhydride (50 ml). The mixture is heated at 90°C during 3 hours. After cooling, the reaction mixture is poured into cold acidic water (500 ml) and the resulting precipitate collected by filtration, washed with water and purified after drying by crystallisation in an appropriate solvent.

7-(2-methylenepropionyl)-2,2-dimethyl-3,4-dihydro-3-oxo-1,4(2H)benzoxazine (5a) : Yield 70% ; mp 174-175°C (from methanol) ; ^{1}H N.M.R : 5.55 (s, 1H) and 5.8 (s, 1H ; $>C=\underline{CH_2}$) ; 9.4 (s,1H)

7-(2-methylenepropionyl)-2,4-dimethyl-3,4-dihydro-3-oxo-1,4(2H)benzoxazine (5b) : Yield 78% ; mp 59-60°C (from n.hexane) ; ^{1}H N.M.R : 4.7 (q,1H).

7-(2-methylenepropionyl)-2,2,4-trimethyl-3,4-dihydro-3-oxo-1,4(2H)benzoxazine (5c) : Yield 78% ; mp 82-83°C (from cyclohexane) ; ^{1}H N.M.R. : 1.50 (s, 6H) ; 3.4 (s, 3H) ; 5.6 (s, 1H) and 5.85 (s, 1H ; $>C=\underline{CH_2}$)

GENERAL PROCEDURE FOR THE SYNTHESIS OF 7-(3-BROMO-2-METHYLPROPIONYL)-2,4-SUBSTITUTED-3,4-DIHYDRO-3-OXO-1,4(2H)BENZOXAZINES (6a-c)

A solution of the α,β unsaturated ketone (5)(0.05mol) in anhydrous chloroform (100ml) was reacted wich gazeous HBr (0.05mole) during 4 hours. If necessary the mixture is filtered and the filtrate evaporated under reduced pressure. The solid residue was then crystallised in an approriate solvent.

7-(3-bromo-2-methylpropionyl)-2,2-dimethyl-3,4-dihydro-3-oxo-1,4(2H)benzoxazine (6a) : Yield 80% ; mp 130-132°C (from methanol); ^{1}H N.M.R 3.4 (d,2H).

7-(3-bromo-2methylpropionyl)-2,4-dimethyl-3,4-dihydro-3-oxo-1,4(2H)benzoxazine (6b) : Yield 80% ; mp 56-57°C (from n.hexane) ; ^{1}H N.M.R : 3.55 (m,2H).

7-((3-bromo-2-methylpropionyl))-2,2,4-trimethyl-3,4-dihydro-3-oxo-1,4(2H)benzoxazine (6c) : Yield 85% ; mp 79-80°C (from n.hexane) ; 1H N.M.R : 3 (m,2H).

GENERAL PROCEDURE FOR THE SYNTHESIS OF 7-(3-CYANO-2-METHYLPROPIONYL)-2,4-SUBSTITUTED-3,4-DIHYDRO-3-OXO-1,4(2H)BENZOXAZINES (7a-c).

The bromo compound (6)(0.03mole) is dissolved by heating in 95° ethanol (80ml). An aqueous solution (10ml) of potassium cyanide (0.35mole) is added and the mixture heated under reflux during 3 hours. After cooling and filtration, the solvent is evaporated,the residue taken up in water (200ml).The resulting solid is filtered and crystallised in an appropriate solvent.

7-(3-cyano-2-methylpropionyl)-2,2-dimethyl-3,4-dihydro-3-oxo-1,4(2H)benzoxazine (7a) : Yield 70% ; mp 178-180°C (from isopropylalcohol); ^{1}H N.M.R 2,60 (m,2H)

7-(3-cyano-2-methylpropionyl))-2,4-dimethyl-3,4 - dihydro-3-oxo-1,4(2H)benzoxazine(7b) : Yield 63% ; mp 115-116°C (from ethanol) ; 1H N.M.R . 2.68 (m,2H).

7-(3-cyano-2-methylpropionyl)-2,2,4-trimethyl-3,4 dihydro-3-oxo-1,4(2H)benzoxazine (7c). Yield 82% ; mp 84°C (from methanol) ; 1H N.M.R . 2.65 (m, 2H).

GENERAL PROCEDURE FOR THE SYNTHESIS OF THE 4-OXO-4-(-2,4-SUBSTITUTED-3,4(2H)BENZOXAZIN-7-YL)-3 METHYLBUTYRIC ACIDS (8a-c).

A suspension of the nitrile (7)(0.03mole) in 5N HCl (80ml) is refluxed during 2 hours. By cooling the acid precipitates; it is filtered, washed with water and crystallised.

4-oxo-4-(-2,2-dimethyl-3,4-dihydro-3-oxo-1,4 (2H) benzoxazin-7-yl)-3-methylbutyric acid (8a) : Yield 60% ; mp 144-150°C (from water) ; 1H N.M.R : 2.5 (d, 1H) and 3 (d, 1H, CH_2 - COOH)

4-oxo-4-(-2,4-dimethyl-3,4-dihydro-3-oxo-1,4 (2H)benzoxazin-7-yl)-3-methylbutyric acid (8b) Yield 80% ; mp 78°C (from cyclohexane) ;1H N.M.R : 2.5 (d, 1H) and 3 (d, 1H, $\underline{CH_2}$ - COOH) ; 4.65 (q, 1H)

4-oxo-4-(-2,2,4-trimethyl-3,4-dihydro-3-oxo-1,4 (2H)benzoxazin-7-yl)-3-methylbutyric acid (8c) : Yield 80% ; mp 145-147°C (from cyclohexane) ; 1H N.M.R : 2.5 (d, 1H) and 3 (d, 1H, CH_2 - COOH)

GENERAL PROCEDURE FOR THE SYNTHESIS OF THE 6-(-2,4-SUBSTITUTED-3,4-DIHYDRO-3-OXO-1,4 (2H)BENZOXAZIN-7-YL)-2,3,4,5-TETRAHYDRO-5-METHYLPYRIDAZIN-3-ONES (9 a-c).

The acid (8)(0.02mole) is dissolved by heating in ethanol (80ml) and hydazine monohydrate (0.04 mole) is added .The mixture is refluxed during 4 hours and then cooled.The solid is collected by filtration,washed with ethanol and crystallised.

6-(-2,2-dimethyl-3,4-dihydro-3-oxo-1,4 (2H) benzoxazin-7-yl)-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (9a) Yield 75% ; mp > 280°C (from ethanol) (289-290°C[10]) ; 1H N.M.R (DMSO) : 1 (d,3H) ; 1.45 (s,6H) ; 2.2 (d,2H) ; 3.45 (m,3H) ; 6.95 (d,1H) ; 7.4 (d,1H); 7.5 (dd,1H) ; 10.6 (s,1H) ; 10.8 (s,1H) ;

6-(2,4-dimethyl-3,4 dihydro-3-oxo-1,4 (2H) benzoxazin-7-yl)-2,3,4,5-tetrahydro-5 methylpyridazin-3-one (9b) : Yield 80% ; mp 260°C (from ethanol); ^1H N.M.R : 3.45(m, $\underline{CH}$-CH_3 and N-$\underline{CH_3}$); 4.7 (q, 1H)

6-(2,2,4-trimethyl-3,4-dihydro-3-oxo-1,4 (2H) benzoxazin-7-yl)-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (9c) : Yield 86% ; mp 220°C (from acetone) (222-224°C[10]); ^1H N.M.R :1.5 (s,6H)

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