SYNTHESIS OF ^{3}H-ETOMIDATE AND RESOLUTION INTO ITS ENANTIOMERS

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Received on April 3, 1975.

SUMMARY

Etomidate, (R)-(+)-ethyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate, is a short-acting hypnotic. Tritium was introduced in the ortho-position of the phenyl-group by catalytic dehalogenation of the 2-chloro-analogue. The homologous tritiated methylester, (+)-methyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate, was hydrolyzed to the corresponding carboxylic acid. The resolution into both enantiomers was carried out by successive salt formation with (R)-(+)- and (S)-(-)-α-methylbenzenemethanamine. After isolation of the diastereoisomeric salts, both enantiomers were obtained by esterification of the salts in ethanol, saturated with HCl-gas.

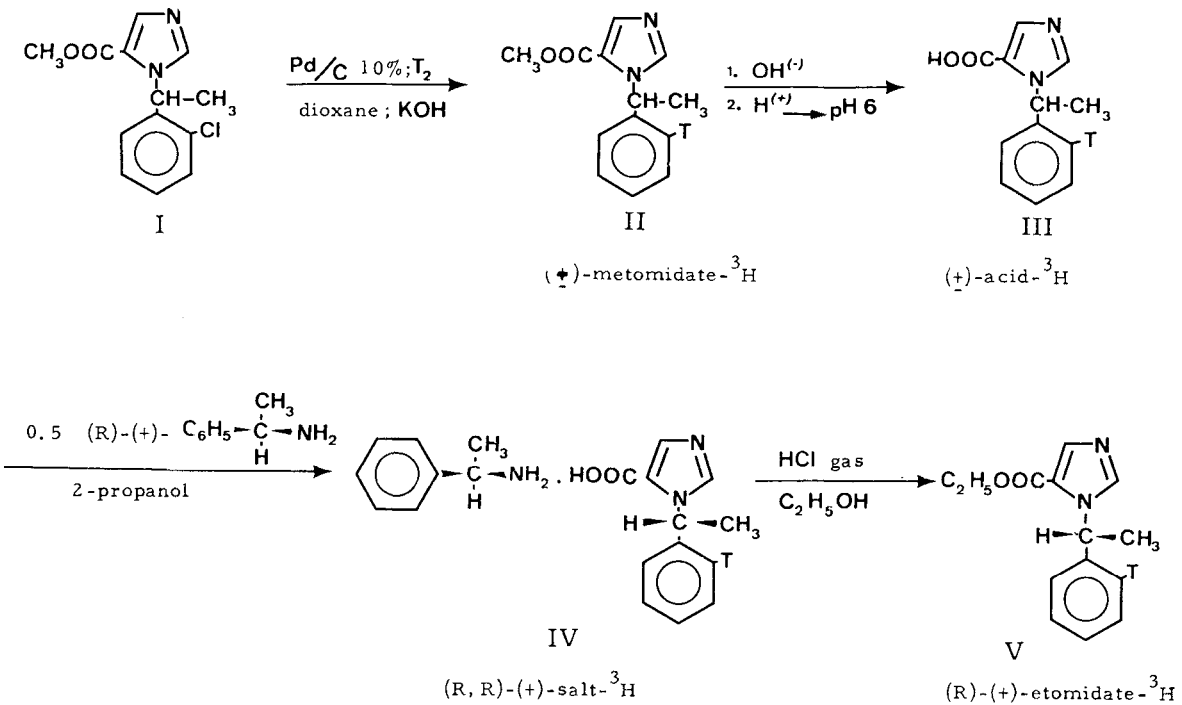
Introduction

Etomidate, (R)-(+)-ethyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate, is a potent, short-acting non-barbiturate hypnotic (1) in experimental animals (2, 3) and in man (4, 5). Only the (R)-(+)-isomer possesses hypnotic activity, the (S)-(-)-compound being pharmacologically inactive (6). In order to get more information about the pharmacokinetics of the enantiomers of etomidate in animals, it was necessary to synthesize both forms of the labelled drug.

Out of several possibilities, the ortho-position of the phenyl-group was chosen as convenient for the tritium label.

The synthesis of racemic etomidate has been described by Godefroi et al. (1). Starting from both enantiomers of labelled α-methylbenzenemethanami-

Scheme A

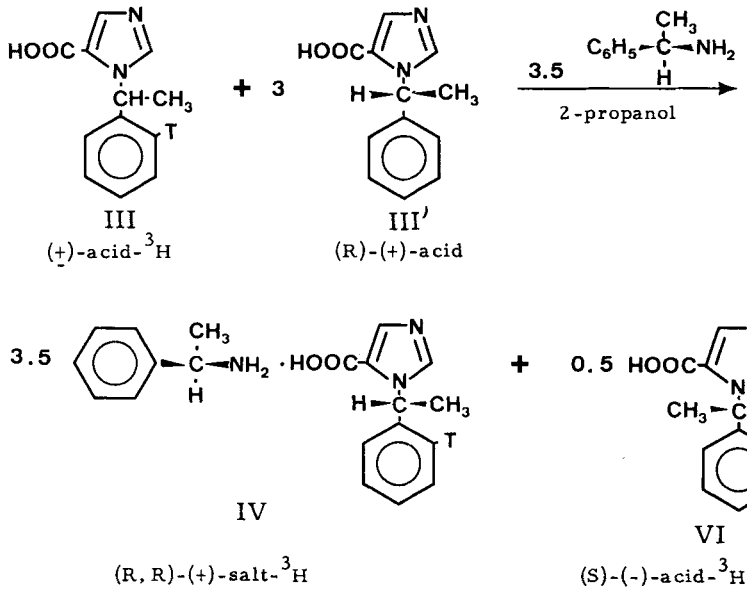

CH3OOC
CH-CH3
Cl
I
Pd/C 10%;T2
dioxane ; KOH
T
II
(±)-metomidate-3H
1. OH(-)
2. H(+) → pH 6
HOOC
III
(±)-acid-3H
0.5 (R)-(+)- C6H5-C(CH3)(H)-NH2
2-propanol
NH2 . HOOC
IV
(R, R)-(+)-salt-3H
HCl gas
C2H5OH
C2H5OOC
V
(R)-(+)-etomidate-3H

ne, it would be possible to obtain the corresponding isomers of etomidate. This procedure would require at least six "radioactive" steps.

The resolution of labelled racemic etomidate, using an optically active acid, proved difficult because of the weak basic properties of the drug (pK_a = 4.24). Therefore, a more convenient method was worked out, which is outlined in Scheme A. This method is based on the resolution of the enantiomeric acid (III), obtained in the hydrolysis of metomidate, i.e. (±)-methyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate (II), followed by esterification of the resolved diastereomeric salts. In order to obtain sufficient amounts of the labelled drug (with a suitable specific activity) and to facilitate the resolution step, unlabelled acid (III') was added to the tritiated racemic compound (III), as shown in Scheme B. The salt formation was carried out using 0.5 mole of the optically active base per mole of the racemic acid.

The (S)-(-)-isomer was isolated from the filtrate after addition of one equivalent of (S)-(-)-α-methylbenzenemethanamine.

Scheme B



Experimental

ANALYTICAL PROCEDURES

Radioactivity measurements

The specific activity of the labelled intermediates and of etomidate was measured by liquid scintillation spectrometry (Packard Tri-Carb 3380, equipped with an automatic activity analyser 544). The radioactivity of the samples was counted in 10 ml of a scintillator solution, containing 5 g of PPO and 0.1 g of dimethyl-POPOP in a 1-litre mixture of toluene/ 2-propanol (8/2, v/v).

Determination of the radiochemical purity

For this purpose, the inverse isotope dilution technique was used. To a known amount of radioactivity, 250 mg of unlabelled etomidate sulphate was added. The solid was dissolved in hot 2-propanol. After addition of a small volume of diisopropylether, etomidate sulphate crystallized on cooling. Further purification was performed by repeated crystallizations from a 2-propanol/diisopropylether mixture (7/3, v/v) until the specific activity of the last three isolates was constant.

In addition to this procedure, the purity was tested by thin-layer chromatography. The labelled compounds, dissolved in methanol (50 μg/50 μl), were chromatographed on silicagel plates (Merck F 254) using a mixture of chloroform/2-butanone (1/1, v/v) as a moving liquid. The radioactivity of the plates was scanned with a Berthold radiochromatogram scanner (LB 2723).

Measurements of specific rotation

The specific rotation $[\alpha]$ of the compounds was measured at 589 nm and 25°C in a Perkin Elmer 141 polarimeter, using 10-cm cells.

SYNTHESIS

Methyl 1-[1-(phenyl-2-t)ethyl]-1H-imidazole-5-carboxylate (II)

To a solution of 0.2 mmole (53 mg) of I in dioxane (0.8 ml)was added successively 30 mg of Pd/C (10%) and 0.2 ml of a methanolic potassium hydro-

xide (1 N) solution. Tritiation* of compound I was performed for 1 hour at room temperature, using 50 Ci of tritium gas. After removal of the catalyst and evaporation of the organic solvent, water (4 ml) was added and the mixture was extracted four times with a small volume of chloroform. About 820 mCi (88% of the total radioactivity present in the mixture) was extracted into the chloroform. After evaporation to dryness, 650 mg of unlabelled metomidate hydrochloride (2.4 mmole) was added and crystallized from a 2-propanol/diisopropylether mixture (7/3, v/v), yielding 598 mg of ^{3}H-metomidate hydrochloride (II), with a specific activity of 339 mCi/mmole.

(±)-1-[1-(Phenyl-2-t)ethyl]-1H-imidazole-5-carboxylic acid (III)

To 598 mg of II (2.2 mmole), dissolved in 2 ml of water, was added 1 ml of a 10 N sodium hydroxide solution and the mixture was warmed up until complete dissolution. After refluxing for 10 minutes, the solution was cooled, acidified with 0.6 ml of glacial acetic acid to pH 6 and the white precipitate was collected and dried, yielding 436 mg (91%) of III, specific activity 330 mCi/mmole.

Resolution of (±)-1-[1-(phenyl-2-t)ethyl]-1H-imidazole-5-carboxylic acid (III). (Scheme B)

To 216 mg of III (1 mmole) was added 648 mg (3 mmole) of unlabelled (R)-(+)-1-(1-phenylethyl)-1H-imidazole-5-carboxylic acid (III') and the mixture was dissolved in 3 ml of hot 2-propanol. After cooling to about 50°C, 0.45 ml (3.5 mmole) of (R)-(+)-methylbenzenemethanamine, dissolved in 1 ml of 2-propanol, was added. After dilution of the solution with 2 ml of water and cooling in an ice bath, the white precipitate was filtered off and washed twice with diisopropylether, yielding 850 mg (71%) of IV, $[\alpha]_D^{25}$ = + 52.6° (C=0.1% in water).

*This reaction was carried out at the I.R.E. (Mol, Belgium).

(R)-(+) Ethyl 1-[1-(phenyl-2-t)ethyl]-1H-imidazole-5-carboxylate sulphate (V)
(R)-(+)-etomidate-^{3}H-sulphate.

In a three-necked flask of 50 ml, 850 mg (2.5 mmole) of IV was suspended in 15 ml of absolute ethanol* and the mixture was saturated with hydrogen chloride gas, dried over concentrated sulphuric acid. The reaction mixture was warmed up in an oil bath of 100°C and HCl gas was passed through the solution for an additional 7 hours. Then the reaction mixture was cooled to room temperature, the organic solvent was evaporated in vacuo and the residual oil was dissolved in 10 ml of water. After adjusting the pH to 6 with sodium hydroxide (10 N) solution, the mixture was extracted with chloroform. The organic layer was filtered over cotton wool, evaporated to dryness, and the residue was dissolved in 1 ml of 2-propanol. The solution was then acidified with concentrated sulphuric acid and, after addition of a few millilitres of diisopropylether, (R)-(+)-etomidate sulphate (V) crystallized on cooling. After isolation and drying of the crystals 674 mg (79%) of V was obtained, $[\alpha]_D^{25} = +21.6°$ (C=1% in methanol). The specific activity was 43 mCi/mmole and the radiochemical purity was more than 98%.

(S)-(-)-Ethyl 1-[1-(phenyl-2-t)ethyl]-1H-imidazole-5-carboxylate nitrate.
(S)-(-)-etomidate-^{3}H nitrate.

The filtrate of the resolution of III (cfr. supra), containing (S)-(-)-1-[1-(phenyl-2-t)ethyl]-1H-imidazole-5-carboxylic acid (VI), was evaporated to dryness and diluted with 280 mg (1.3 mmole) of the unlabelled (S)-(-)-acid. The mixture was dissolved in hot 2-propanol and 218 mg (0.23 ml) of (S)-(-)-methylbenzenemethanamine was added. Further preparation of the (S)-(-)-enantiomer was analogous to the preparation described for V. The compound was isolated as the nitrate salt (crystallization from toluene), yielding 225 mg (≈40%) of (S)-(-)-etomidate-^{3}H nitrate. The specific rotation of the nitrate

* dried for 3 days over molecular sieve 4 Å (Merck) and magnesium powder.

salt was $[\alpha]_D^{25} = -23.9°$ (C= 1% in ethanol) and the specific activity was 92 mCi/mmole. The compound was radiochemically pure as tested by thin-layer chromatography and the inverse isotope dilution technique.

Acknowledgements

The authors wish to thank Dr. M. Winand of the I. R. E. (Mol, Belgium) for performing the catalytic tritiation and Mr. J. Thyssen for technical assistance.

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