SYNTHESIS OF 2 DEUTERIUM LABELLED ANALOGS OF VERALIPRIDE

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SUMMARY

Veralipride was labelled with trideuteromethyl groups first in the o-methoxy and later in both o-and m-methoxy positions respective to the benzamide functions. Hydroxylated benzaldehydes were the starting materials and $(CD_3)_2SO_4$ the labelling substance. A known synthesis was followed for veralipride-d_3. This synthesis was extensively modified in the final steps for veralipride-d_6 by introducing an ester exchange reaction which increased the overall yield.

KEYWORDS

Veralipride,
orthomethoxybenzamide,
deuterium labelled.

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INTRODUCTION

Veralipride, 5-(Sulfamoyl)-N-[(N-allylpyrrolidinyl)-2-méthyl]-2,3-dimethoxybenzamide, a new non-hormonal and non-steroïdal compound with anti-dopaminergique and anti-gonadotrophic activity[1-3], is used to control "hot flushes" and other physiological disturbances during menopause.

The pharmacokinetic parameters have been previously determined in our Laboratory [4-5].

These pharmacokinetic studies as well as ongoing metabolic transformation studies required the use of labelled compounds. Our choice was to incorporate the stable isotope deuterium into the molecule. Thus veralipride-d_3, 5-(Sulfamoyl)-N-[(N-allylpyrrolidinyl)2-methyl]-2-trideuteromethoxy-3-methoxy benzamide, VIa, Figure I, and veralipride-d_6, 5-(Sulfamoyl)-N-[(N-allylpyrrolidinyl)2-methyl]-2,3-trideuteromethoxybenzamide, VIb, Figure I, were synthesized.

EXPERIMENTAL

A. Veralipride d_3

2-trideuteromethoxy-3-methoxybenzaldehyde (Ia)

In a 100 ml flask with magnetic stirring 17 ml H_2O and 2-hydroxy-3-methoxybenzaldehyde (12.8 gr, 0.076 mole) were added and the mixture heated to 60°C. When this temperature was reached 8.5 ml of 30% NaOH were added to the mixture and immediately after $(CD_3)_2SO_4$ (10 gr, 0.076 moles) was introduced. The reaction mixture was refluxed for 10 min. The mixture was cooled to 60°C and 4.3 ml of 30% NaOH and immediately after (5,0 gr, 0.038 moles) $(CD_3)_2SO_4$ was added. The mixture was refluxed again for 10 min at 60°C, 1.7 ml of 30% NaOH were added and the mixture refluxed for 15 min. After cooling to 20°C the mixture was stirred for 12 hrs. The precipitate was filtered, washed

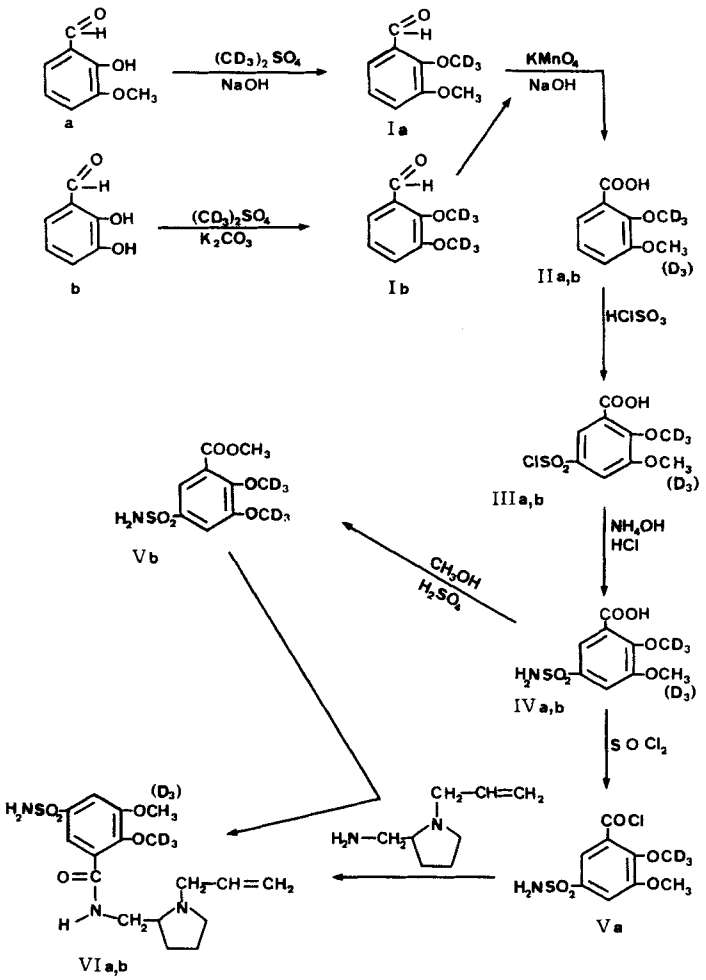

FIGURE 1 : Reaction scheme for the synthesis of veralipride-d_3 and veralipride-d_6.

and recrystalized in ethanol. The yield was 97.3% ; m.p. 50-52°C ; the IR spectrum (BECKMAN, 4230) showed absorptions at 1682 cm^{-1} (C=O), 2070, 2125, 2195, 2230, 2255 cm^{-1} ($-OCD_3$), 1580 cm^{-1} (C=C) ; NMR spectrum (δ, $CDCl_3$) : 10.48 (1H singlet CHO), 7.08-7.59 (3H multiplet, aromatic protons) 3.90 (3H singlet OCH_3).

B. Veralipride-d_6

2,3-trideuteromethoxybenzaldehyde (Ib)

In a flask containing 2,3-dihydroxybenzaldehyde (5.74 g, 0.041 mole), K_2CO_3 (10.43 g, 0.076 mole) dissolved in 80 ml of anhydrous acetone, $(CD_3)_2SO_4$ (10 g, 0.076 mole) was added under magnetic stirring. The mixture was heated at 60°C for five hours. After evaporation of the acetone the residue was redissolved and alkalinized by 0.1 N NaOH. This aqueous phase was extracted three times with $CHCl_3$ and the organic phase containing product (Ia) were dried over $MgSO_4$. After evaporation of the $CHCl_3$ under reduced pressure, the product (Ia) was recrystallized from petroleum ether (bp 40-60°C). The yield was 79% ; m.p. 52-53°C ; I.R. spectrum showed absorption at : 3080 cm^{-1} (-C=C-), 2870, 2760 cm^{-1} (CHO), 2260, 2230, 2198, 2128, 2075 cm^{-1} (OCD_3), 1680 cm^{-1} (C=O), 1588 cm^{-1} (C-H aromatic) ; NMR spectrum : (δ, $CDCl_3$), 7.18 (2H doublet, j=4Hz, aromatic protons) 7.5 (1H triplet, j=4Hz, aromatic protons), 10.48 (1H singlet, CHO).

2,3-ditrideuteromethoxy-5-sulfamoyl methylbenzoate (Vb)

In a flask containing dry methanol (11.9 ml, 0.295 mole) and concentrated H_2SO_4 (0.78 ml, 0.78 mole) the sulfamide (IVb), (3.8 g, 0.0147 moles) was added. The mixture was heated at reflux (60-70°C) for 5 hrs. After evaporation of the methanol under reduced pressure the residue was dissolved in water and made alkaline by K_2CO_3, the mixture

was chilled by ice chips. The ester was then extracted from the alkaline aqueous phase by $CHCl_3$. After drying and evaporation of the organic phase the crystalline residue was the ester (Vb). The yield was 80% ; m.p. : 141-142°C ; I.R. spectrum showed absorption at : 3360, 3265 cm^{-1} ($-NH_2$), 3100 cm^{-1} (CH, aromatic), 3960 cm^{-1} (CH, ester), 2270, 2240, 2180, 2130, 2075 cm^{-1} (OCD_3), 1330, 1150 cm^{-1} (SO_2), 1735 cm^{-1} (C=O) ; NMR spectrum : (δ, DMSO-d_6/$CDCl_3$ 50/50) 3.95 (3H singlet, CH_3), 6.06 (2H broad singlet, NH_2), 7.72 (1H doublet, j=2.4Hz, aromatic proton), 7.95 (1H doublet, j=2.4Hz, aromatic proton).

Veralipride d_6 (VIb)

The ester (Vb) (3 g, 0.011 mole) was added by small fractions to an excess of N-allyl-2-aminomethyl-pyrrolidine (6.17 g, 0.0440 mole) under strirring at room temperature. The mixture was stirred for 12 hrs at room temperature in a closed flask.

The varalipride-d_6 was separated from the excess of the side chain by successive acid and alkaline extractions with $CHCl_3$. After the organic phase was dried and evaporated the veralipride-d_6 then was recovered from diisopropyl ether with a few drops of methanol, and further recrystallized from benzene. The yield was 60 % ; m.p. : 99-100°C ; I.R. spectrum showed absorptions at 3440-3120 cm^{-1} ($CONH-NH_2$), 3080 cm^{-1} (aromatic CH), 2975 cm^{-1} (CH), 2260, 2235, 2195, 2130, 2080 cm^{-1} (OCD_3), 1640 cm^{-1} (C=O), 1535 cm^{-1} (CONH), 1325, 1160 cm^{-1} (SO_2) and 1085, 1055 (OCD_3) ; NMR spectrum (δ, $CDCl_3$) : 1.75 (4H singlet, $-CH_2-CH_2$), 1.95-4.00 (7H multiplet, CH_2, CH_2, CH_2, CH), 4.88-5.43 (2H multiplet, $=CH_2$), 5.43 (2H broad singlet, NH_2), 5,5-6.51 (1H multiplet =CH-), 7.56 (1H doublet, j=2.2Hz, aromatic proton), 8.2 (1H doublet, j=2.2Hz, aromatic proton), 8.27 - 8.67 (1H multiplet (NH).

DISCUSSION

The overall reaction scheme for the synthesis of veralipride as developed by Laboratoires Delagrange is presented in Figure I along with our own modifications. This synthesis was followed directly and only our own modifications are detailed. All synthetic intermediates were isolated as white crystalline products whose identities were confirmed by melting points, I.R., NMR and GC-MS.

The OCD_3 groupements were introduced at the first step of the synthesis. The starting materials were 2-hydroxy-3 methoxybenzaldehyde for veralipride-d_3 and 2,3-dihydroxybenzaldehyde for veralipride-d_6. The labelled starting material was in both cases $(CD_3)_2SO_4$ with an isotopic purity of 98.0 %. An alkaline reaction medium was necessary for the methylation of 2,3-dihydroxybenzaldehyde in order to avoid oxidation side products.

The final a steps in the synthesis of veralipride-d_6 were different.

The acid IVb was transformed into the methylester Vb instead of the corresponding acid chloride. The main reason for this was the facility in obtaining the methylester (Vb) over the acid chloride (Va). Care had to be taken, when the time of reaction for the esterification was longer than 5hrs because of transesterification between methanol and the deuterated methoxy groupements which decreased the isotopic purity. Which of the two methoxy groupements is exchanged first and at what rate is under investigation. Veralipride-d_6 was obtained by ester exchange of the compound (Vb) and the pyrrolidine side chain.

The isotopic purity of veralipride-d_3 and veralipride-d_6 as their trimethylated derivatives were verified by GC-MS in CI/NH_3 mode on a NERMAG R10-10 GC-MS system (NERMAG, RUEIL-MALMAISON, FRANCE).

REFERENCES

1 - Czyba J.C., Girod C., - Rev. Fr. Gynēcol. Obstēt. 76 : 667-680 (1981).

2 - Perrault G., Margarit, J., Laville C., - Rev. Fr. Gynēcol. Obstēt. 76, 655-660 (1981).

3 - Olever C., Contedevolx B., Gillioz P., Giraud P., Orlando M., - Rev. Fr. Gynēcol. Obstēt., 76, 681-687 (1981).

4 - Staveris S., Houin G., Tillement J.P., Jamet G., Schneider M., Jung L., Koffel J.C., - J. Pharm. Sci. 74/1 94-96 (1985).

5 - Plusquellec Y., Campistrom G., Staveris S., Jung L., Tillement J.P., Barrē J., Houin G., - J. Pharmacokin. Biopharm. submitted January 1985.

6 - Laboratoires Delagrange - Fr. Patent 2 358 892 (1976).

7 - Staveris S., Jung L., Jamet G., Koffel J.C., - J. of chrom., Biom. Appl. 338, 79-88 (1985).