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(54) Title: PROCESS FOR THE SYNTHESIS OF HIGH PURITY D-(17ALPHA)-13-ETHYL-17HYDROXY-18,19-DINOR-PRE:GN-4-ENE-20-YNE-3-ONE-OXIME

(57) Abstract: The invention relates to a process for the synthesis of high purity d-(17α)-13-ethyl-17hydroxy-18,19-dinorpregn-4-ene-20-yne-3-one-oxime (further on norelgestromine) via acetylation of d-norgestrel at position 17, oximation of the oxo group at position 3 of the obtained 17-acetoxy derivative, and finally hydrolyzing the acetoxy group at position 17 of the obtained 3-oxime derivative. The process according to our invention is as follows: the starting material, d-(17α-17-hydroxy-13-ethyl-18,19-dinorpregn-4-ene-20-yne-3one (d-norgestrel) - purity 93-94 % - is acetylated with acetic anhydride in acetic acid, in the presence of zinc chloride and hydrogen chloride, or 70 % perchloric acid in an inert gas atmosphere, and after completion of the reaction the excess of acetic anhydride and the "enol acetate" by-product are decomposed with aqueous hydrochioric acid, then the formed d-(17α)-17-acetoxy-13-ethyl-18,19-dinorpregn-4-ene-20-yne-3-one is isolated from the reaction mixture by addition of ice-water, the precipitated product is filtered off, washed with water, dried, dissolved in dichloromethane or acetone and clarified with silica gel or aluminum oxide and charcoal, after filtration of the clarifier the resulted solution is concentrated and the residue is recrystallized, the obtained d-(17α)-17-acetoxy-13-ethyl-18,19-dinorpregn-4-ene-20-yne-3-one is reacted either with hydroxylammonium acetate or with hydroxylammonium chloride in the presence of sodium acetate, in acetic acid in nitrogen atmosphere under vigorous stirring for about 1 hour, after completion of the reaction water is added, the precipitated product is filtered off, washed with water, dried and recrystallized, the obtained d-(17α-17-acetoxy-13-ethyl-18,19-dinorpregn-4-ene-20-yne-3-one-oxime is hydrolyzed with an equivalent amount of an alkali metal hydroxide in a C_1-C_4 alkanol solution, in nitrogen atmosphere between a temperature of about 5-38 °C, under vigorous stirring, after completion of the reaction the mixture is diluted with water and the pH of the resulted suspension is adjusted to 7,5-9 with acetic acid, the precipitated product is filtered off, washed with water, dried, the crude product is dissolved in ethanol, clarified with charcoal, and after filtration of the clarifier water is added to the obtained solution, the precipitated high purity d-(17α)-17-acetoxy-13-ethyl-18,19-dinorpregn-4-ene-20-yne-3-one-oxime is filtered off, washed with water and in given case recrystallized from ethanol.

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