THE SYNTHESIS OF [^{14}C]-LABELLED ICI 118,551

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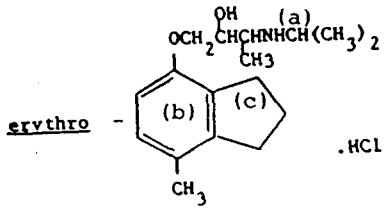
ICI 118,551; erythro-1-(7-methylindan-4-yloxy)-3-isopropyl-aminobutan-2-ol monohydrochloride, a novel β-adrenoceptor antagonist with relative selectivity for the β_2-adrenoceptor has been radiolabelled with [^{14}C] for use in metabolism studies. [^{14}C]-ICI 118,551 was prepared a) from 2-amino [2-^{14}C]propane monohydrochloride in a one stage synthesis at a specific activity of 3.09 mCi/mM and an overall radiochemical yield of 40.1%, b) from p-[ring U-^{14}C]cresol in six stages at a specific activity of 5.9 mCi/mM and an overall radiochemical yield of 14.0% and c) from 3-chloro-[1-^{14}C]-propionyl chloride in six stages at a specific activity of 0.93 mCi/mM and an overall radiochemical yield of 3.8%. The radiochemical purity in all three syntheses was greater than 99%. The synthesis of the major metabolite of ICI 118,551 (the carboxylic acid) is also described as well as the synthesis of some hydroxylated derivatives used in an attempt to identify several of the urinary metabolites of ICI 118,551.



(a), (b) and (c) denote position of [^{14}C]-label

SYNTHESIS OF (6,7-^{3}H) NORETHISTERONE OXIME ACETATE AND ITS APPLICATION

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Norethisterone oxime acetate (17α-ethynyl-17β-acetoxy-19-nor-androst-4-en-3-one oxime) is a perspective contraceptive drug. The antifertility activity is much higher than its parent compound (Norethisterone). In order to study its pharmacokinetics, (6,7-^{3}H)Norethisterone oxime acetate (1) and its metabolic products: (6,7-^{3}H)Norethisterone acetate (2), (6,7-^{3}H)Norethisterone oxime (3) and (6,7-^{3}H)Norethisterone (4), were synthesized by multistage organic reactions. Using 19-Nor-androst-4,6-diene-3,17-dione as a precursor, (6,7-^{3}H) 19-Nor-androst-4-en-3,17-dione (5) was synthesized at first. Then, 4 was synthesized from 5. 3 and 2 were prepared from 4. Finally, 1 was obtained from 2. All the tritiated products were purified by silica gel loaded paper chromatography. The radiochemical purities checked by radio-HPLC and radio-PC are all over 98%. The specific activities of 1 and 5 are 1.6 and 1.9 TBq/mmol, respectively. According to ^{3}H-NMR, it was shown that the tritium lost is mainly on position 6 during the period of reactions from 5 to 1. 1 was used as tracer to determine blood concentration in vivo or in vitro. The one of high specific activity (1.6TBq/mmol) was applied for RIA, and the another of low specific activity (37MBq/mg) was administrated to rabbits. The blood samples containing 1 and its metabolic products were collected at different intervals over a period of 24 hrs, which were separated and analyzed by radio-HPLC method. The pharmacokinetic parameters can be calculated from the curve of time vs blood concentration.