NOTE

A CONVENIENT SYNTHESIS OF [METHYLENE-^2H AND ^3H]TOLAZOLINE

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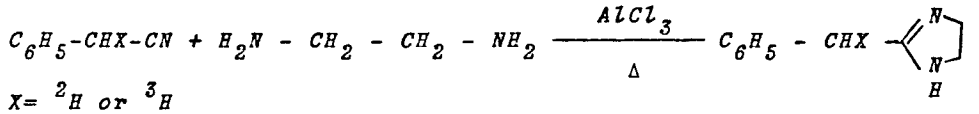

C_6H_5-CHX-CN + H_2N - CH_2 - CH_2 - NH_2 $\xrightarrow[\Delta]{AlCl_3}$ C_6H_5 - CHX - (imidazoline ring)

X= ^2H or ^3H

Drugs labelled with either radioactive or stable isotopes have found wide use in studies of drug metabolism. Befor labelling, the choice of isotope and the site(s) to be labelled are important considerations(1). It has been found that hydrogen (^2H and ^3H) labelling can readily be achieved and total cost are also low. Tolazoline(2-benzylimidazoline) is an α-adrenergic agent and acts pharmacologically as a peripheral vasodilator. Little is known about the fate of Tolazoline in the body. We now report a convenient synthesis of deuterated and tritiated Tolazoline, labelled in the methylene group by addition of ethylenediamine to α-deuterated and α-tritiated phenylacetonitrile in the presence of $AlCl_3$(2).

Experimental

[methylene-^2H and ^3H]benzyl cyanide(3)

To benzyl cyanide(0.15ml) was added dioxan (0.3ml), deuterated water(0.5ml) and anhydrous sodium bicarbonate (25mg). After 24h at 60°C the mixture was cooled and extracted with ether and the extract was dried over Na_2SO_4. Removal of the solvent gave the deuterated product. Preparation of [α- ^3H]benzyl cyanide was carried out ad above using tritiated water(40μl; 5 Ci/ml) and a specific activity of 80mCi/mmol was obtained.

[^2H and ^3H] Tolazolines(2)

Ethylenediamine(2.7ml) and deuterated benzyl cyanide(4.5g) was added to a 100 ml three-necked flask equipped with a condenser, a thermometer and a stirrer. The mixture was shaken

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for ½ hour and $AlCl_3$(5g) was then slowly added. The temperature was maintained below 40°C. Aft er the addition, the reaction mixture was heated to 210°C during which time the solid liquefies. The reaction mixture was then added to dilute HCl(5%; 100ml) stirred and filtered. The filtrate was treated with active charcoal(1g) and filtered. The resulting solution was then neutralized by addition of dilute sodium hydroxide(5%) and the Tolazoline free base was extracted with CH_2Cl_2.Distillation of the residue at 180°/10mm gaue 4.8g(ca.75%)deuterated Tolazoline. Deuterated Tolazoline hydrochloride(mp.174°C) was prepared by the passage of HCl gas through a solution of Tolazoline in ethyl acetate. Tritiated Tolazoline was also prepared as above, but in a micro-scale system (sp.ac.76mCi/mmol).

For N.M.R. analysis of the deuterated and non-deuterated drugs, a 10mg sample was dissolved in a deuterated solvent, a trace of TMS was added and the 'H' spectra recorded at 60 MHz employing a Varian T-60spectremeter. The relative intensities of the corresponding ^1H NMR peaks for unlabelled and labelled materials were determined. The amount of incorporated label was thus calculated at 78%(4).

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