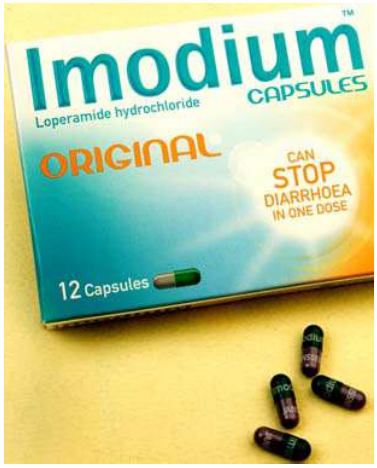
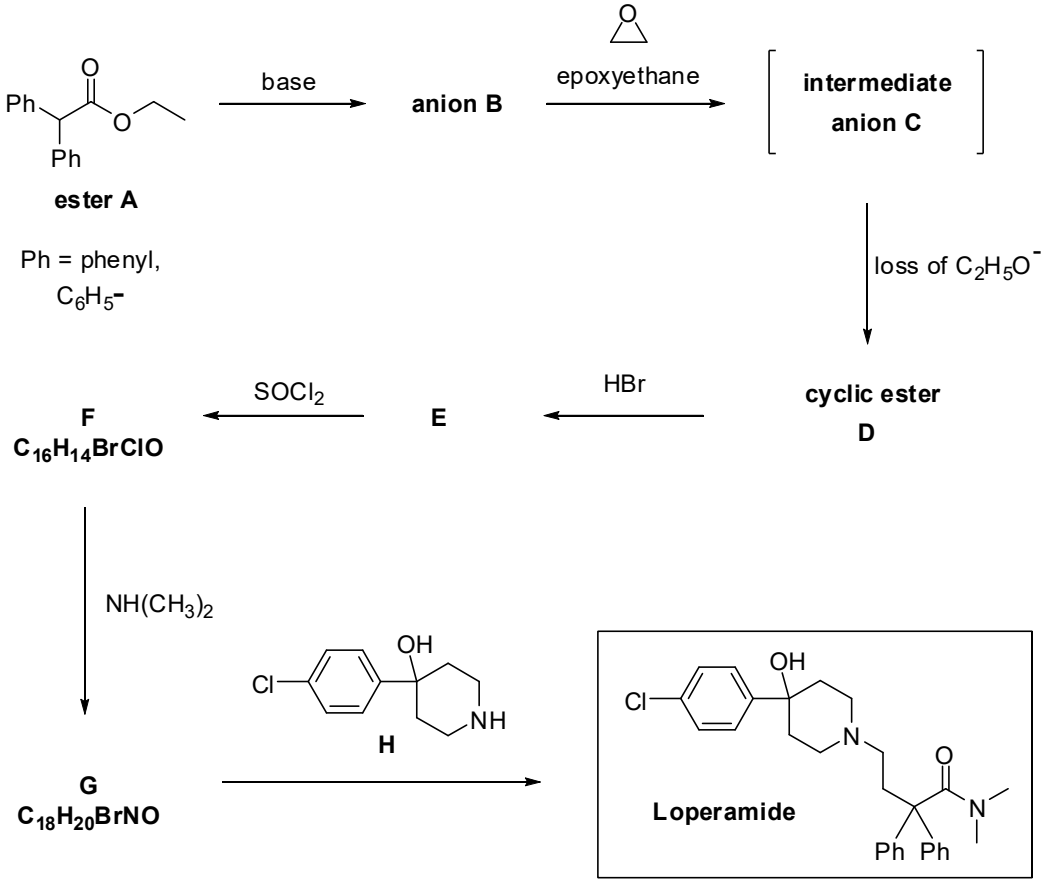
4. This question is about stopping diarrhoea



The active ingredient in anti-diarrhoea medicines such as imodium, is *loperamide*, whose structure is given below. As with many drugs, loperamide is often sold as the hydrochloride salt since this is more soluble in water.

(a) On the structure in your answer booklet, circle the atom in loperamide which will be protonated in the salt.

A synthesis of loperamide is shown below.



(b) (i) Ester **A** may be made by treating a mixture of an alcohol and a carboxylic acid with a catalytic quantity of concentrated sulfuric acid. Give the structures of the alcohol and carboxylic acid.

(ii) Ester **A** is deprotonated by a base to give the anion **B**. Draw the structure of **A** and indicate clearly which proton is removed by the base to form anion **B**.

Anion **B** then opens up the three-membered ring of epoxyethane to form an intermediate, anion **C**. This intermediate then cyclizes and eliminates ethoxide, $C_2H_5O^-$, to form ester **D**.

(c) Draw the structures of anion **C** and cyclic ester **D**.

Ester **D** reacts with bromide which opens the ring to give carboxylic acid **E**. **E** then reacts with $SOCl_2$ to give **F**.

(d) Draw the structures of compounds **E** and **F**.

F reacts with dimethylamine to form **G**. Two isomeric structures may be drawn for **G**; either an open-chain amide, or a cyclic bromide salt. There are *ten* signals in the ^{13}C NMR spectrum of the cyclic bromide salt.

(e) Suggest structures for **G** in (i) the amide form and (ii) the bromide salt form.