

## Study Question 3d

KEY

This problem considers part of the synthetic route to physostigmine, the anti-glaucoma, acetylcholinesterase-inhibiting compound prepared by Percy Julian. This synthesis is the reason for the DePauw being designated as a National Historical Chemistry Landmark (see the plaque in the atrium).

1. Add mechanistic arrows and lone pairs where needed to the scheme on the other side. Fill in the missing structures and any arrows needed on the missing structures. No protons or water are shown. Please provide these where necessary.
2. On the scheme, two parallel routes are shown which both lead to the final product. For this question, please focus on the step marked by the large arrow.
  - (a) At neutral pH, which route do you think will be followed? Concisely explain your answer.

At neutral pH route B will be followed. That's because at neutral pH the  $\text{L-CH}_2\text{NHMe}$  will actually be  $\text{L-CH}_2\text{NH}_2^+\text{Me}$  because we are well below its  $\text{pK}_a$ . In comparison,  $\text{Ar-NHMe}$  is a much weaker base and will not be protonated. Only N w/ a lone pair can be

- (b) Let's say the pH were lowered to 2. Which route will be more favorable under these conditions? Explain concisely.

For the rxn shown at the big arrow, neither route should be operating as both N's would be protonated and hence not nucleophilic.

nucleophiles

