

# Cardiotonics

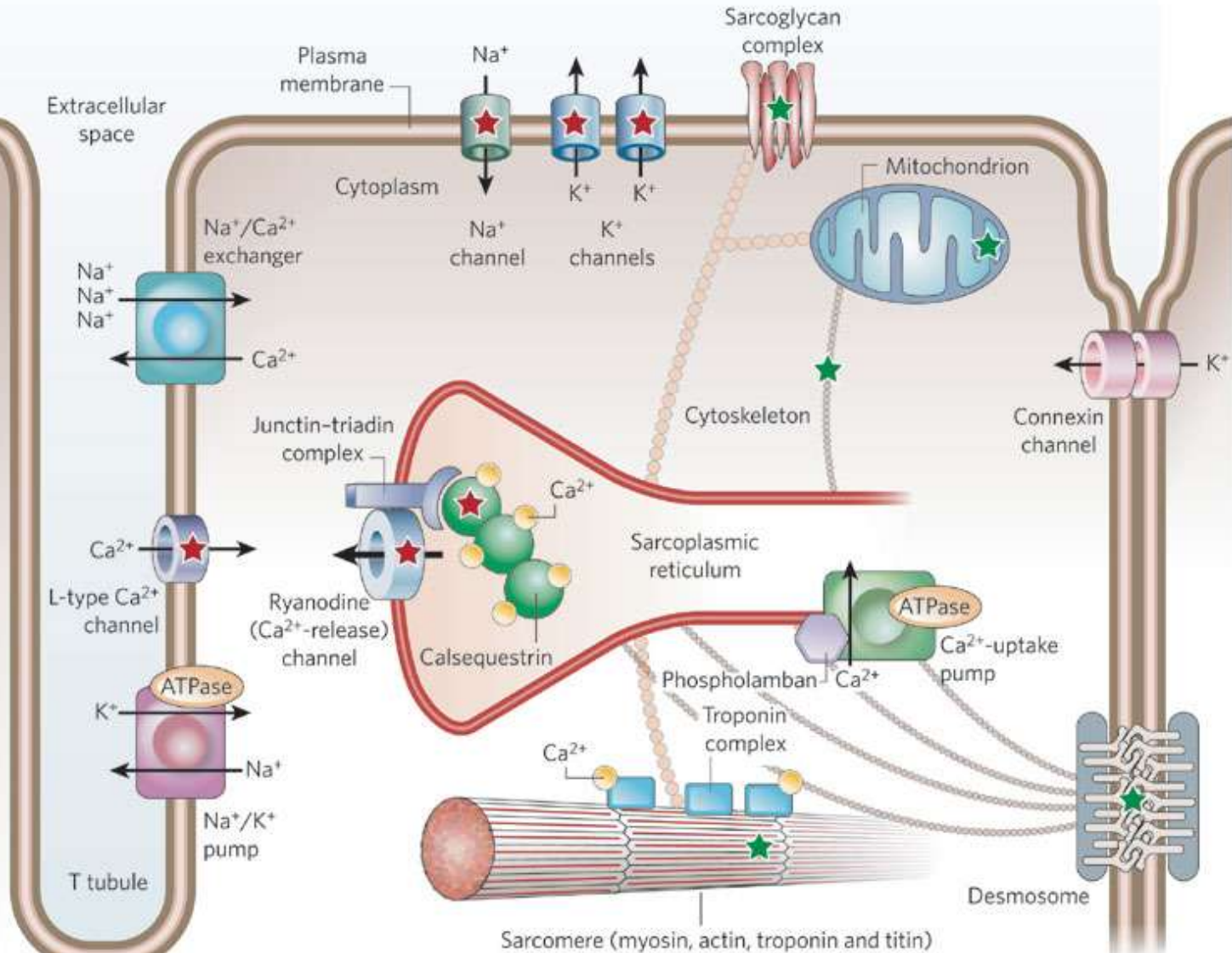
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Tomáš Goněc

12.11.2012



# Cardiomyocyte contraction



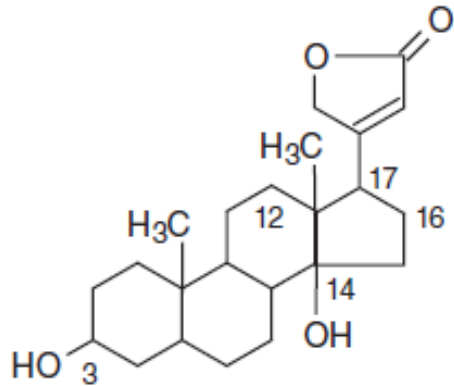
# Therapy of heart failure: inotropic agents

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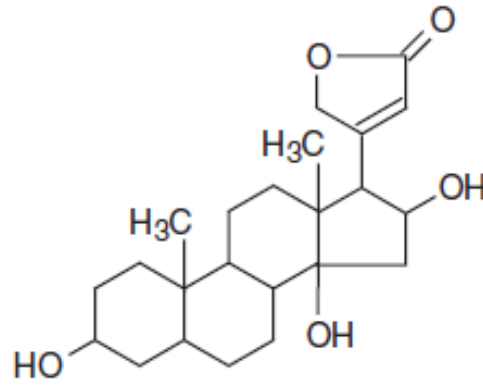
- cardioglycosides
- $\beta$ -adrenergic agonists
- phosphodiesterase inhibitors
- $\text{Ca}^{2+}$  channel sensitzers

# Cardiac glycosides

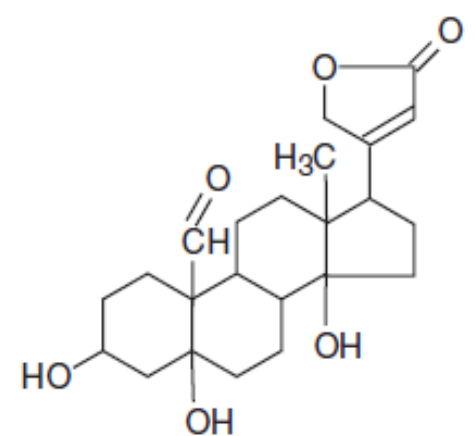
## □ Aglycons:



digitoxigenin

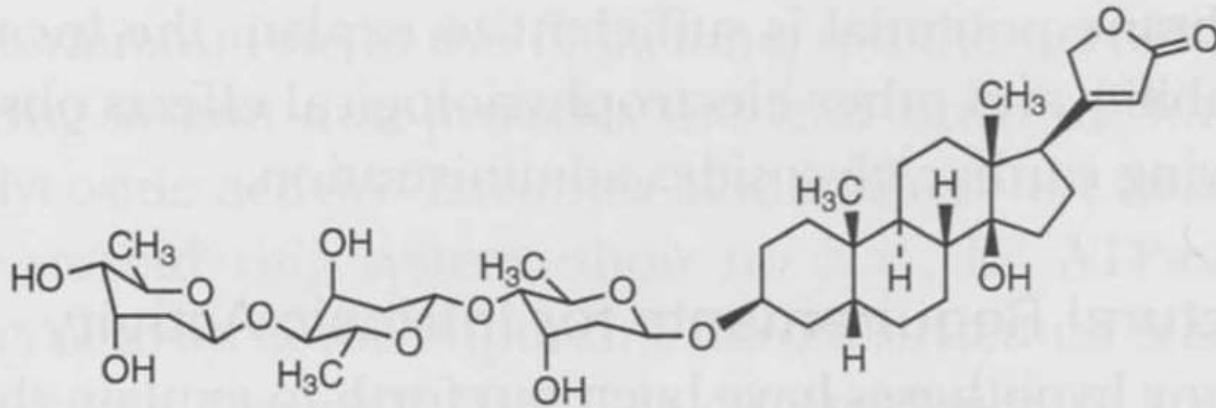


gitoxigenin

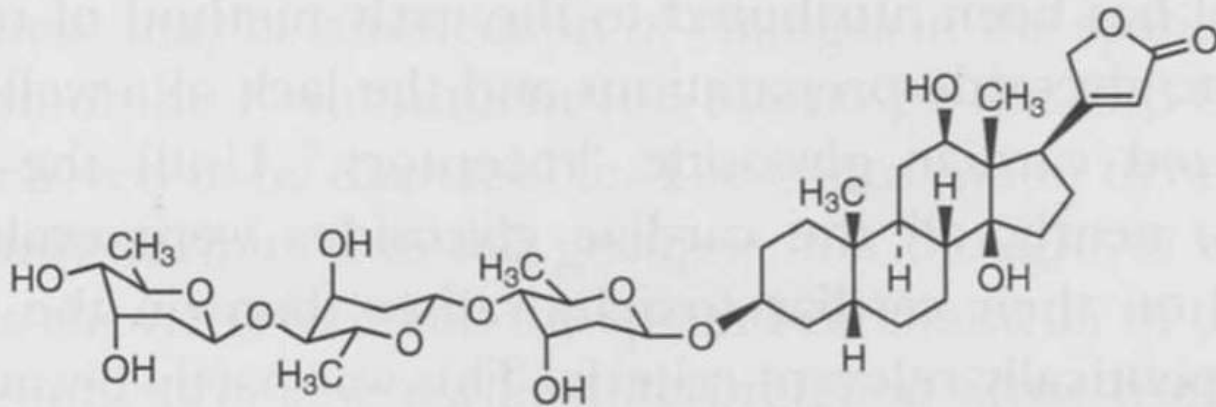


strophanthidin

# Cardiac glycosides



Digitoxin



Digoxin



# Cardiac glycosides – mechanism of action

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- $\text{Na}^+/\text{K}^+$ -ATPase inhibitors
- $\text{Na}^+$  ions intracellular retention
- due to ion substitution also  $\text{Ca}^{2+}$  intracellular retention
- positive inotropic effect

# Cardiac glycosides used in therapy

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- Lanatosides A, B, C; purpureaglycosides A, B  
digitoxin, gitoxin, digoxin – secondary  
glycosides with cleavaged terminal sugar
- Ouabain, k-strophanthoside
- Proscillaridine, meproscillarine  
(buffadienolides)





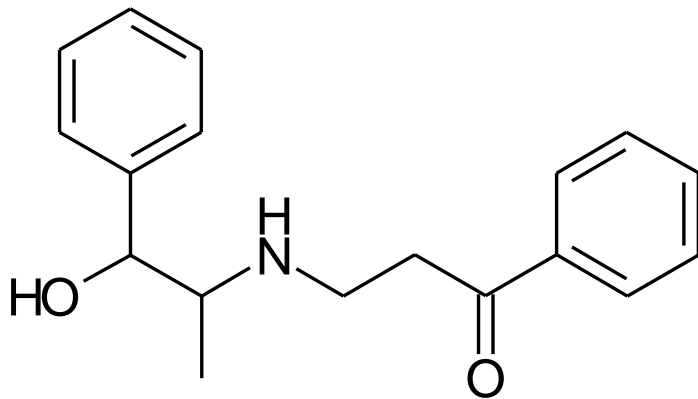
# Cardiac glycosides

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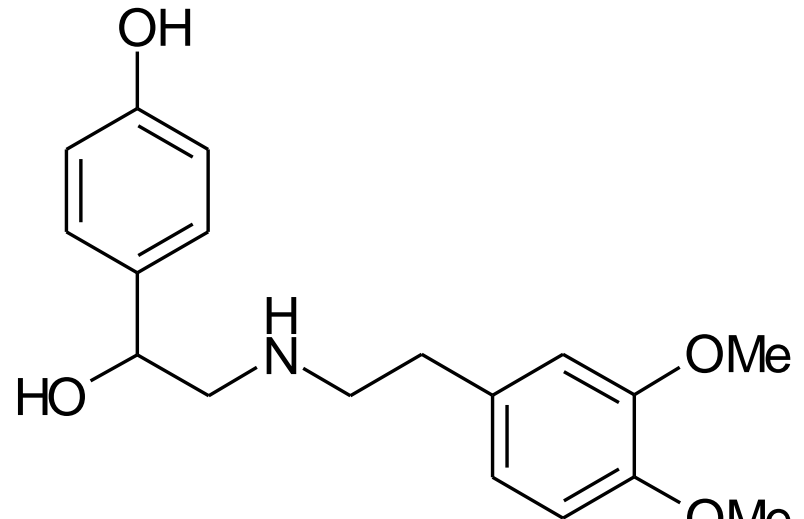
- ❑ narrow therapeutic-toxic window
- ❑ high plasma proteins binding
- ❑ monitoring during therapy necessary
- ❑ long-term administration increases mortality –  
therapeutic use in future questionable

# $\beta_1$ -adrenergic receptor agonists

- stimulation of adenylate-cyclase, increase of intracellular cAMP, positive inotropic effect



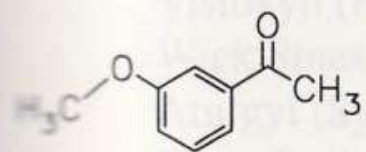
oxyfedrine



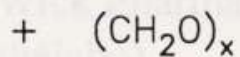
denopamine

# Oxyfedrine synthesis

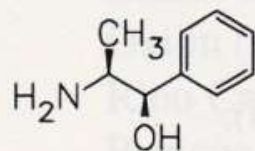
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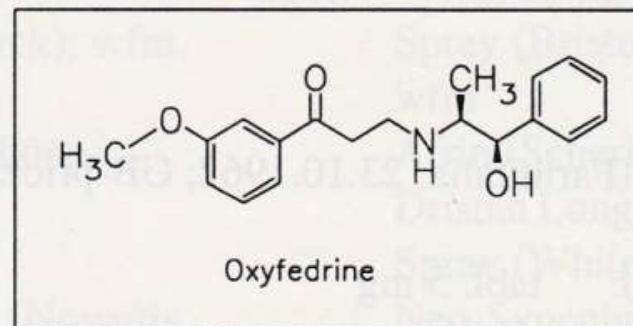
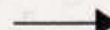
3-methoxyaceto-  
phenone



paraform-  
aldehyde

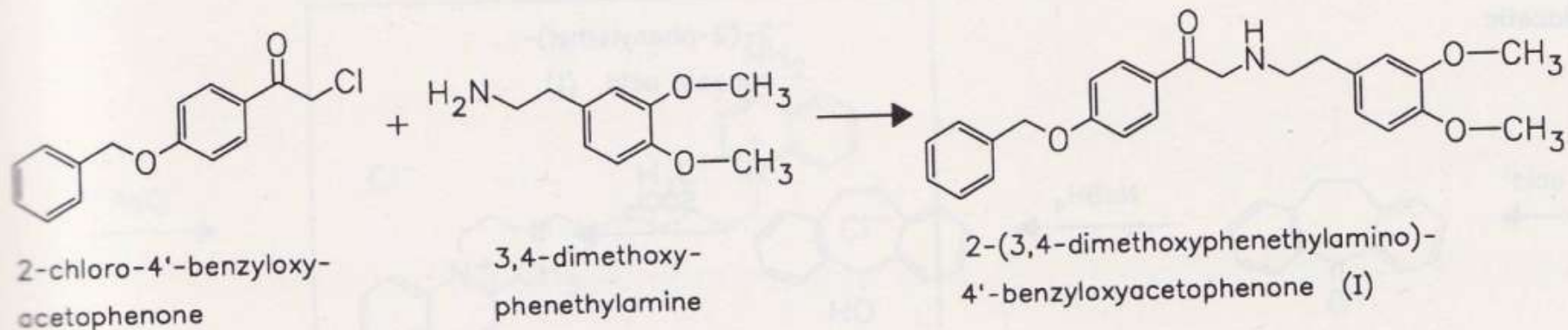


L-norephedrine

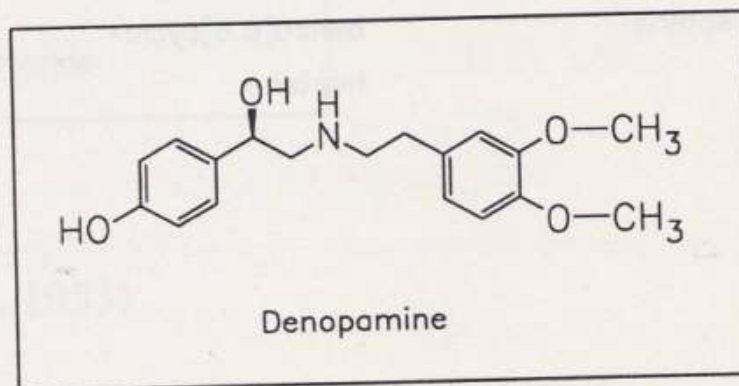


Oxyfedrine

# Denopamine synthesis

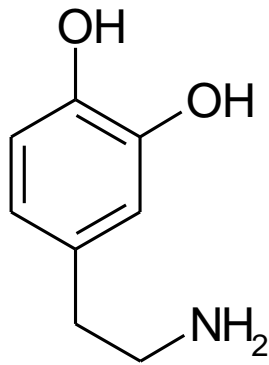


1.  $\text{NaBH}_4$
2. racemate resolution with D(-)-acetylphenylalanine
3.  $\text{H}_2$ , Pd-C

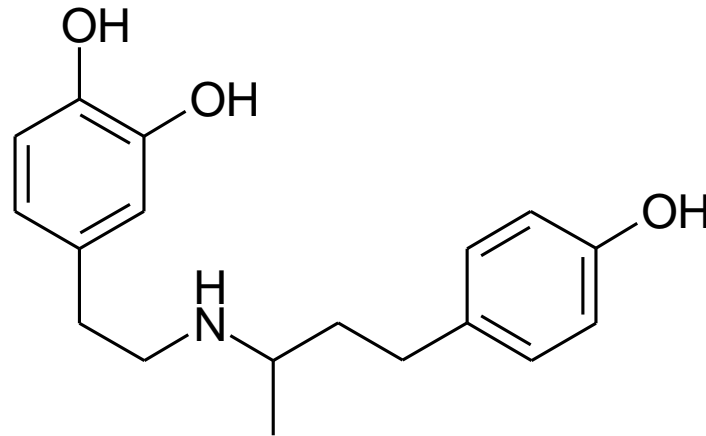


# $\beta_1$ -adrenergic receptor agonists

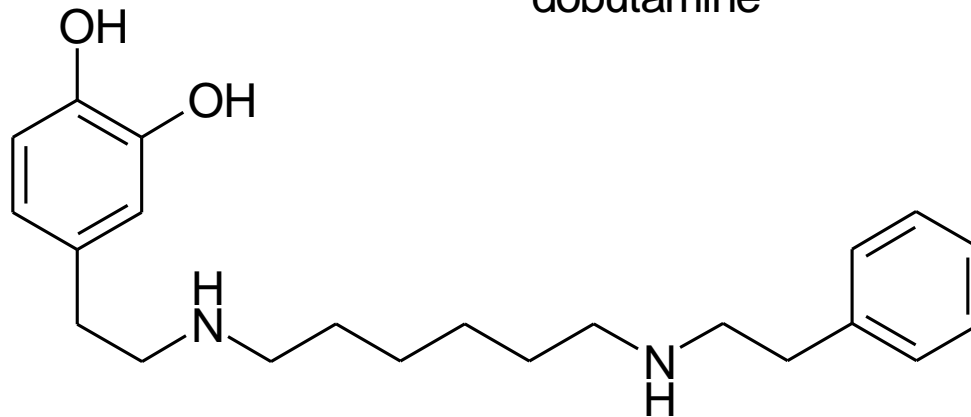
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dopamine

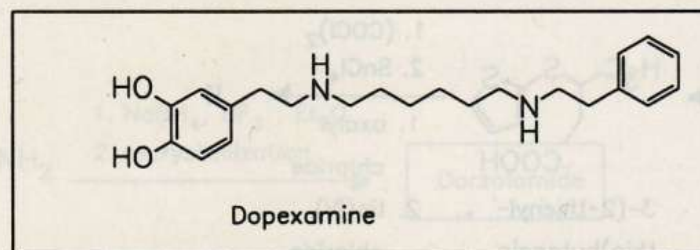
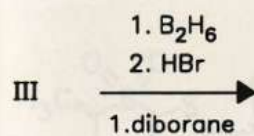
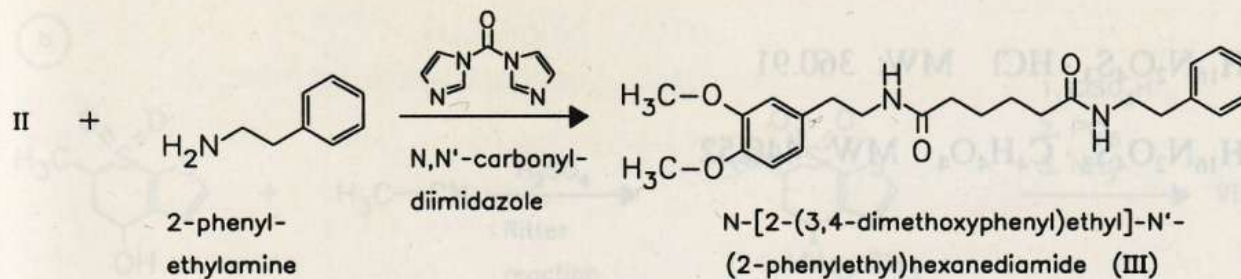
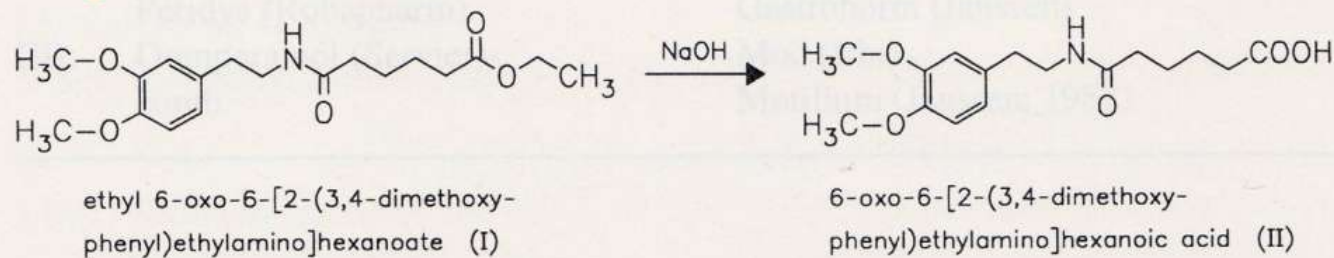
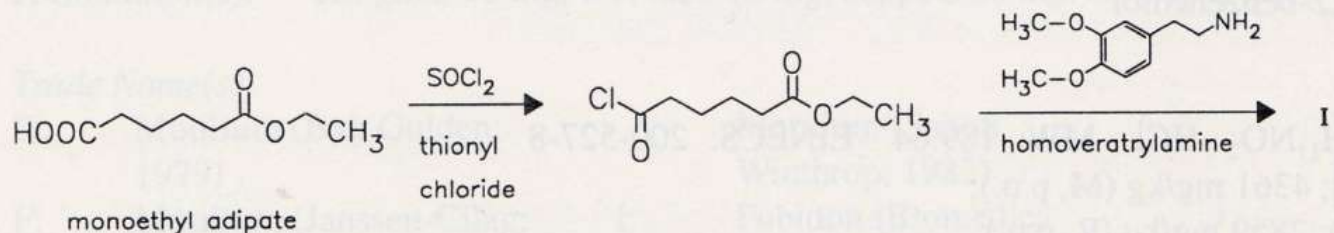


dobutamine



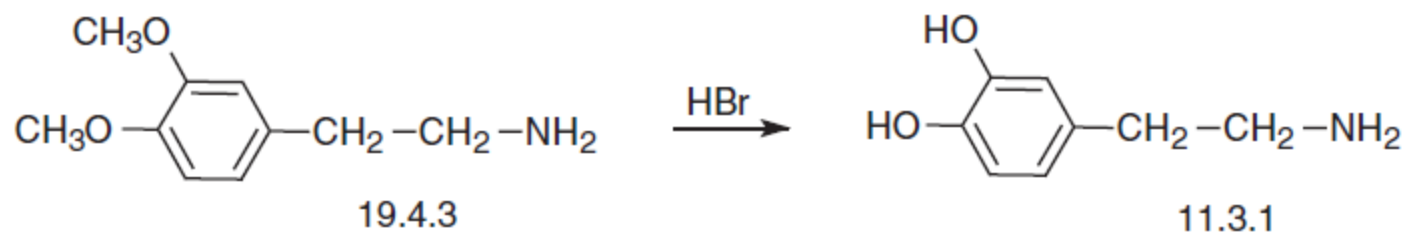
dopexamine

# Dopexamine synthesis

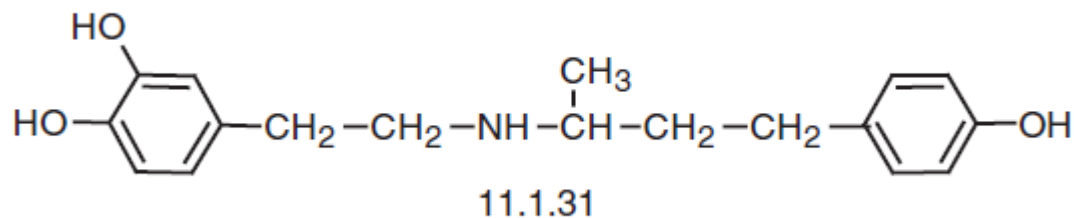
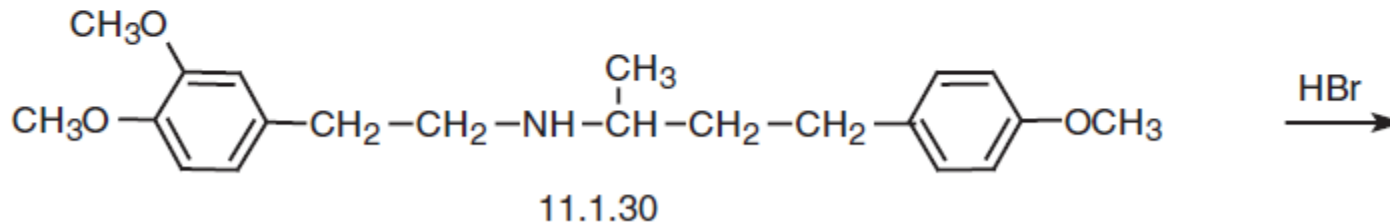
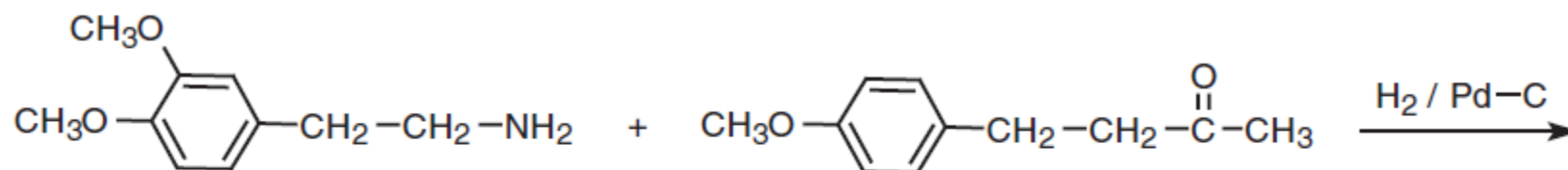


# Dopamine synthesis

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# Dobutamine synthesis







# Phosphodiesterase inhibitors

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- xanthine derivatives
- bipyridine derivatives
- 3-pyridazinone derivatives
- chinolin-2-one derivatives



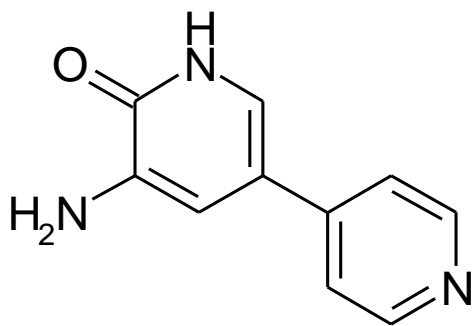
# Xanthine derivatives

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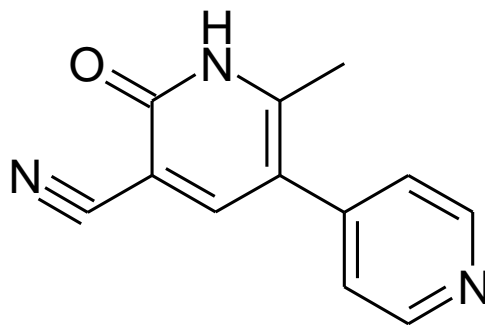
- Theophylline
  - Aminophylline
  - Etophylline
- \* see coronary vasodilators presentation

# Bipyridine derivatives

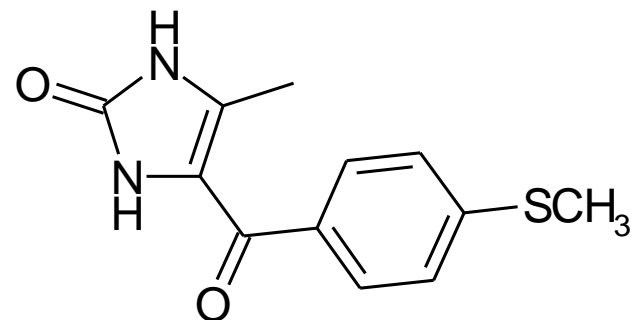
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Amrinon

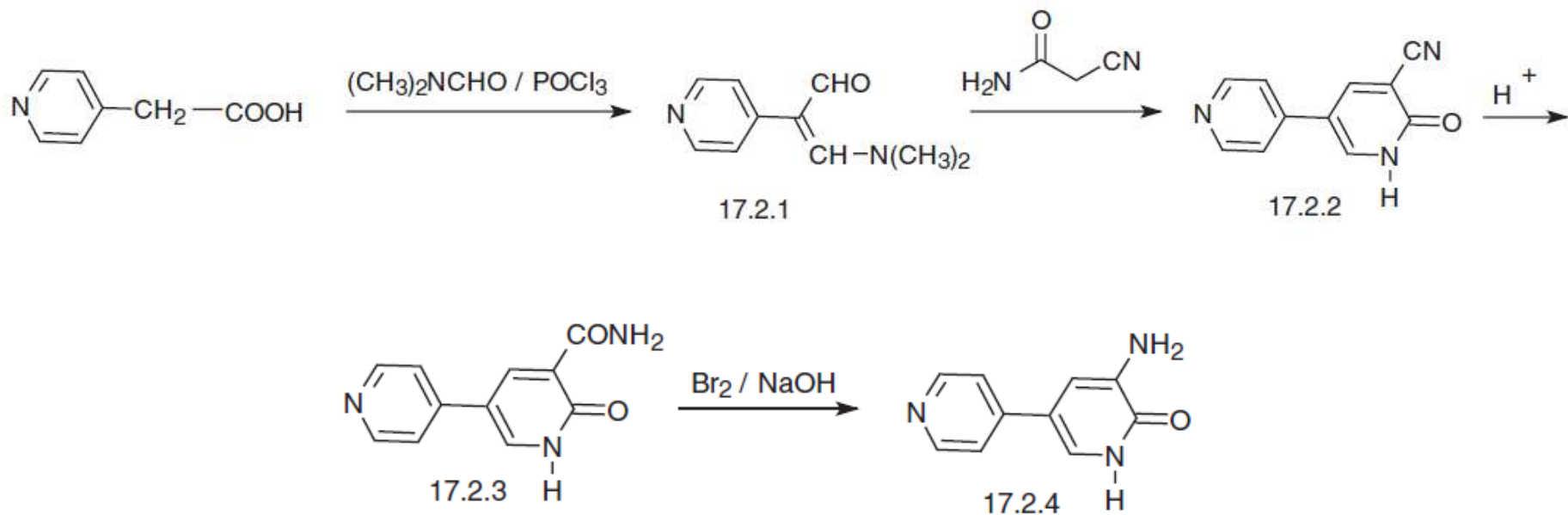


Milrinon



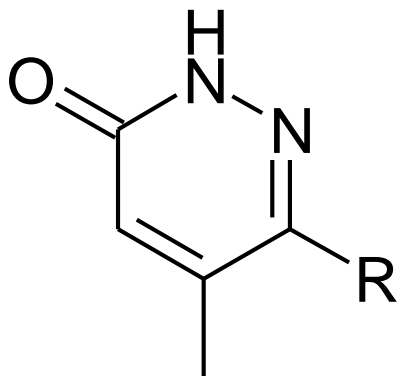
Enoximion

# Amrinon synthesis

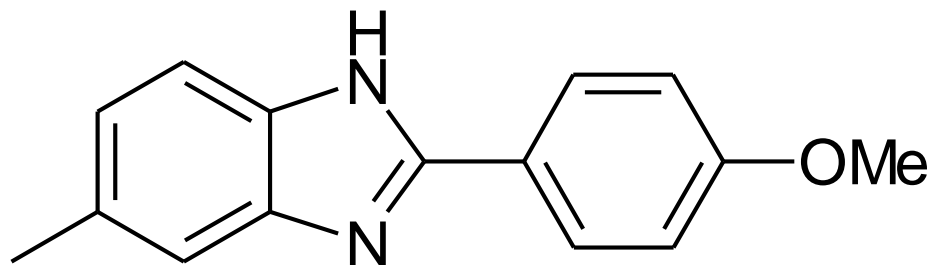


# 3-pyridazinone derivatives

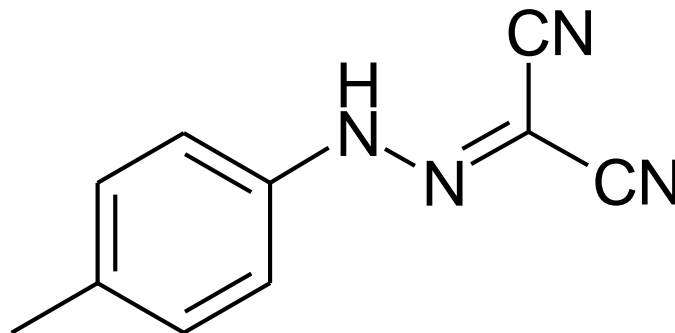
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R:

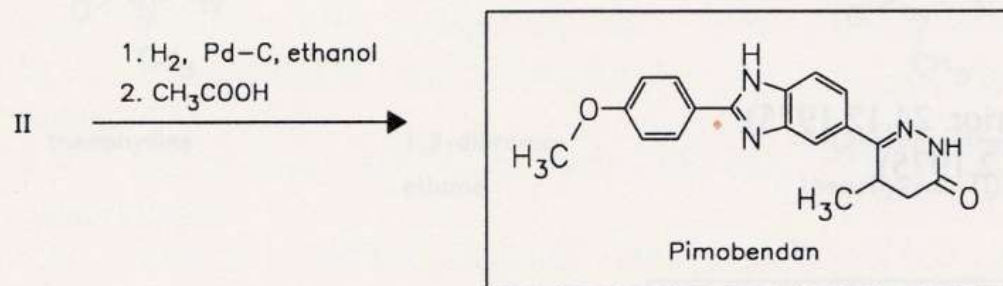
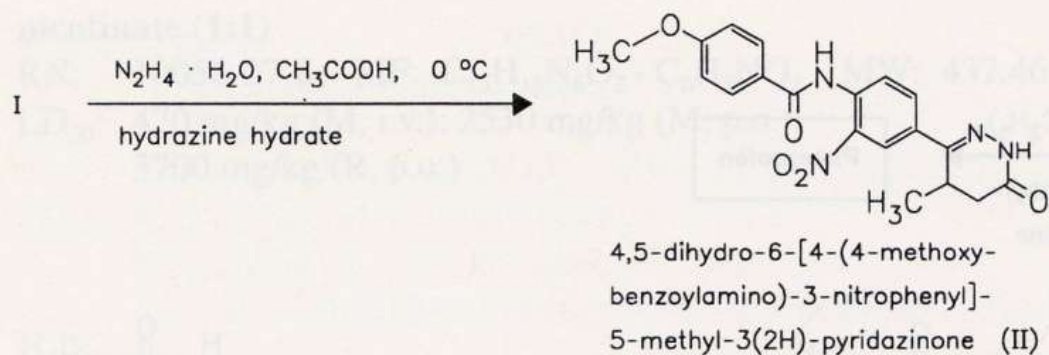
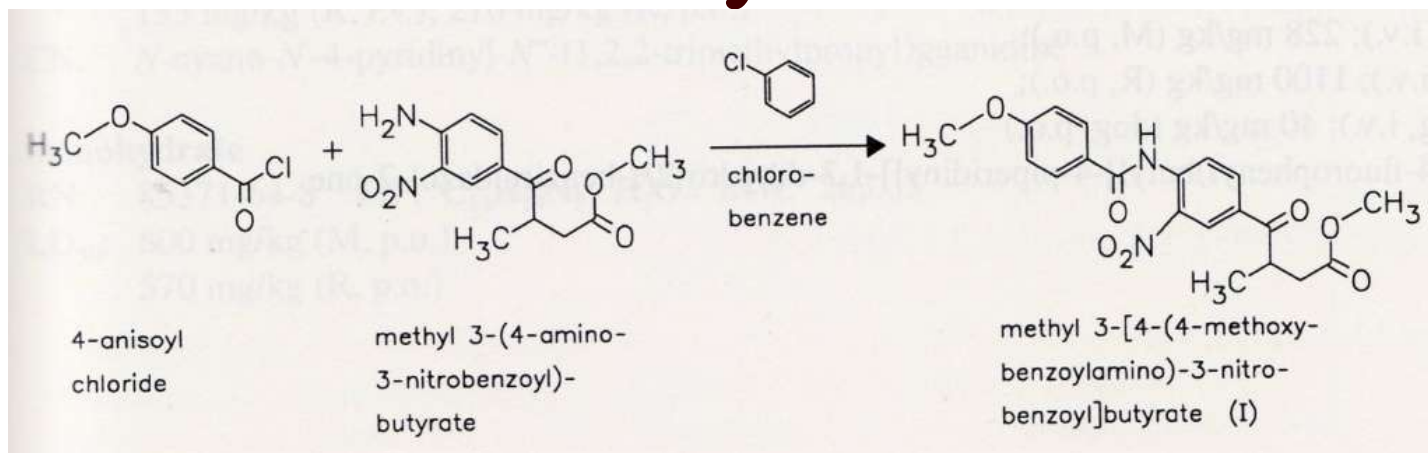


Pimobendan



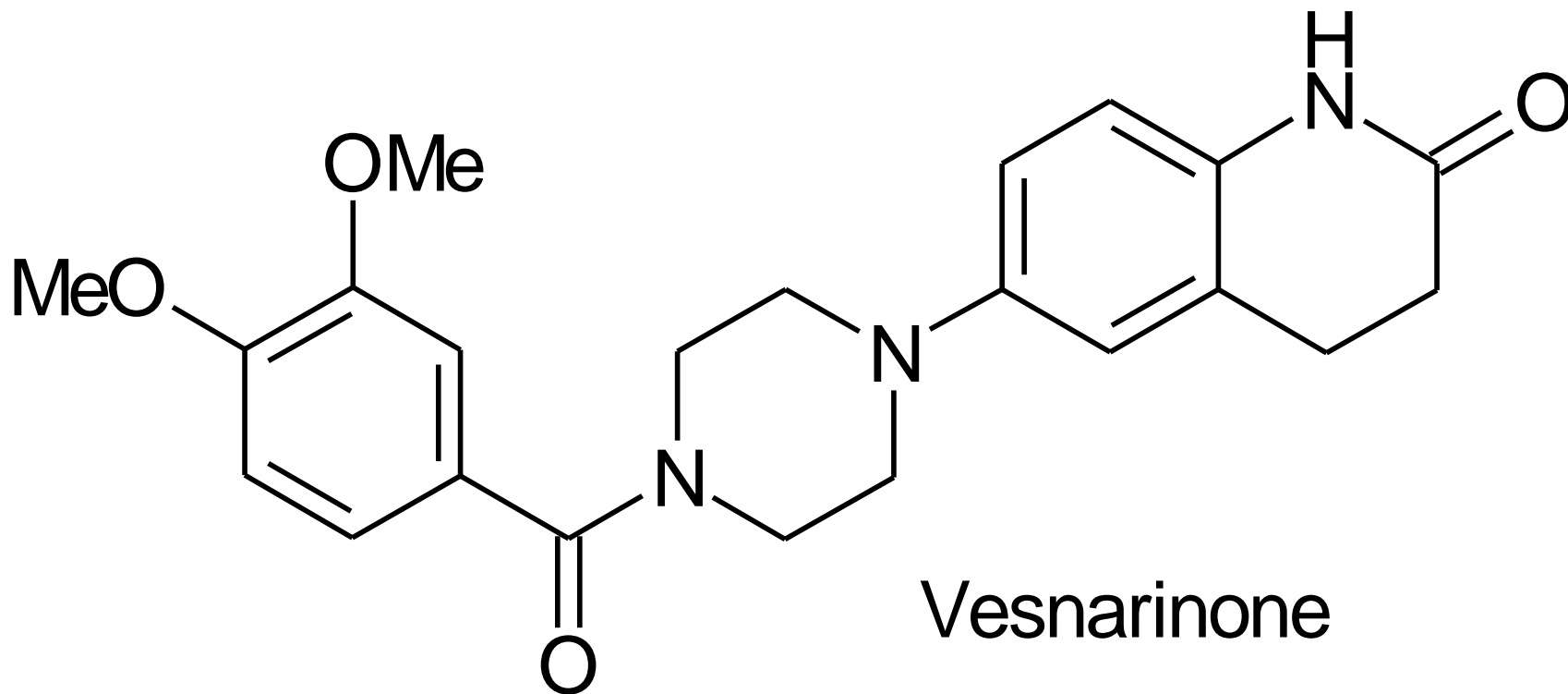
Simendan

# Pimobendan synthesis

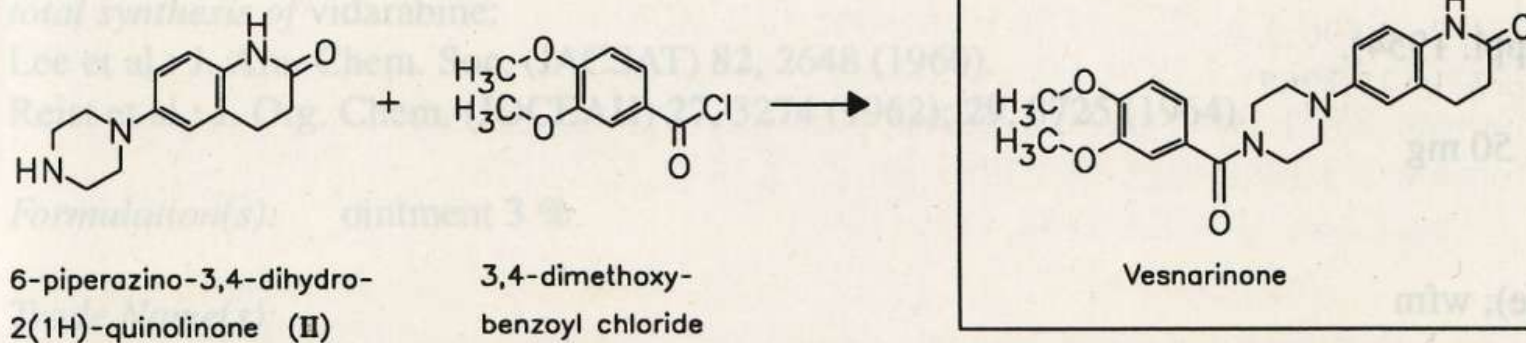
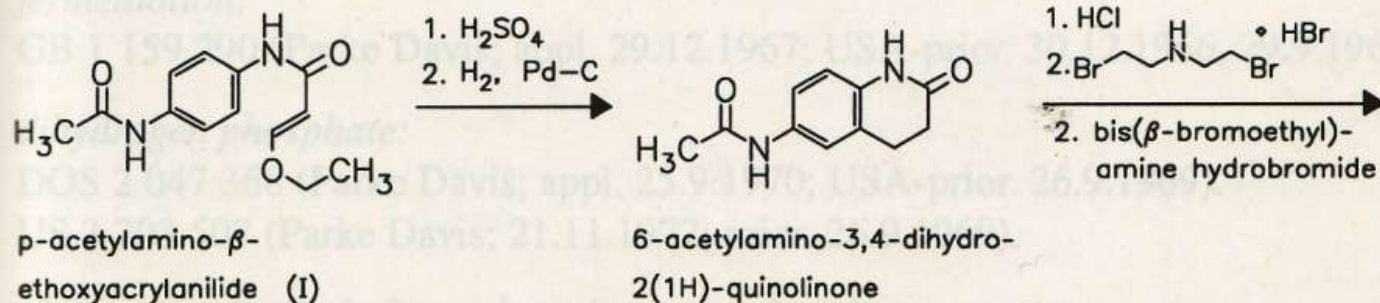
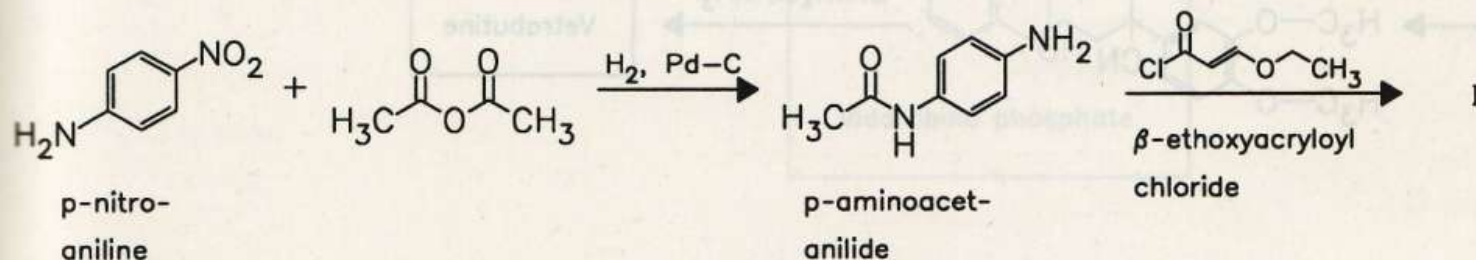


# Chinolin-2-one derivatives

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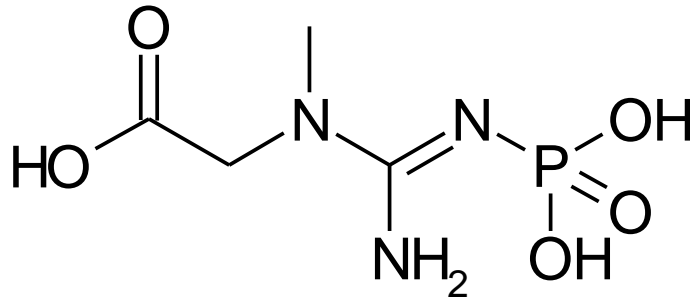
# Vesnarinone synthesis



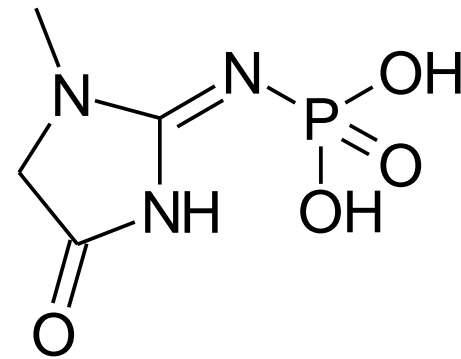


# Cardioprotectives

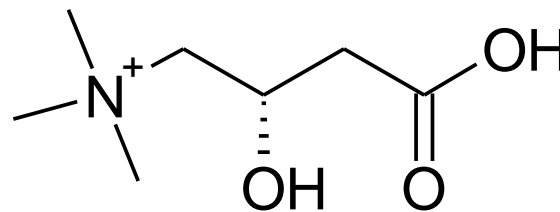
- detoxication of free radicals (NO, OO, OH)



phosphocreatin



phosphocreatinin



L-carnitin