Antiarrhythmics

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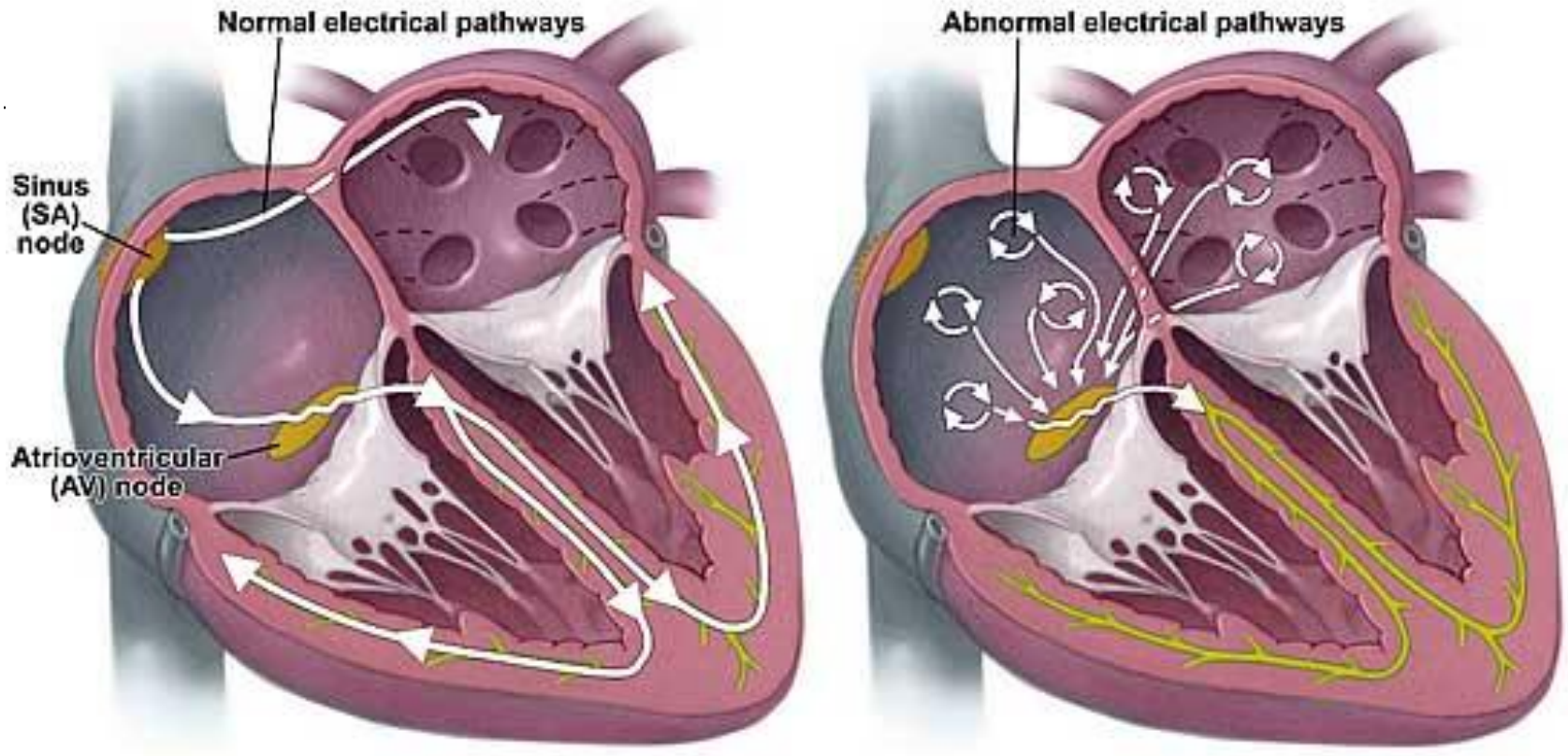
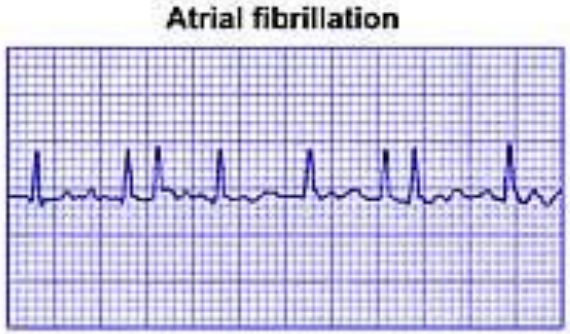
Arrhythmia

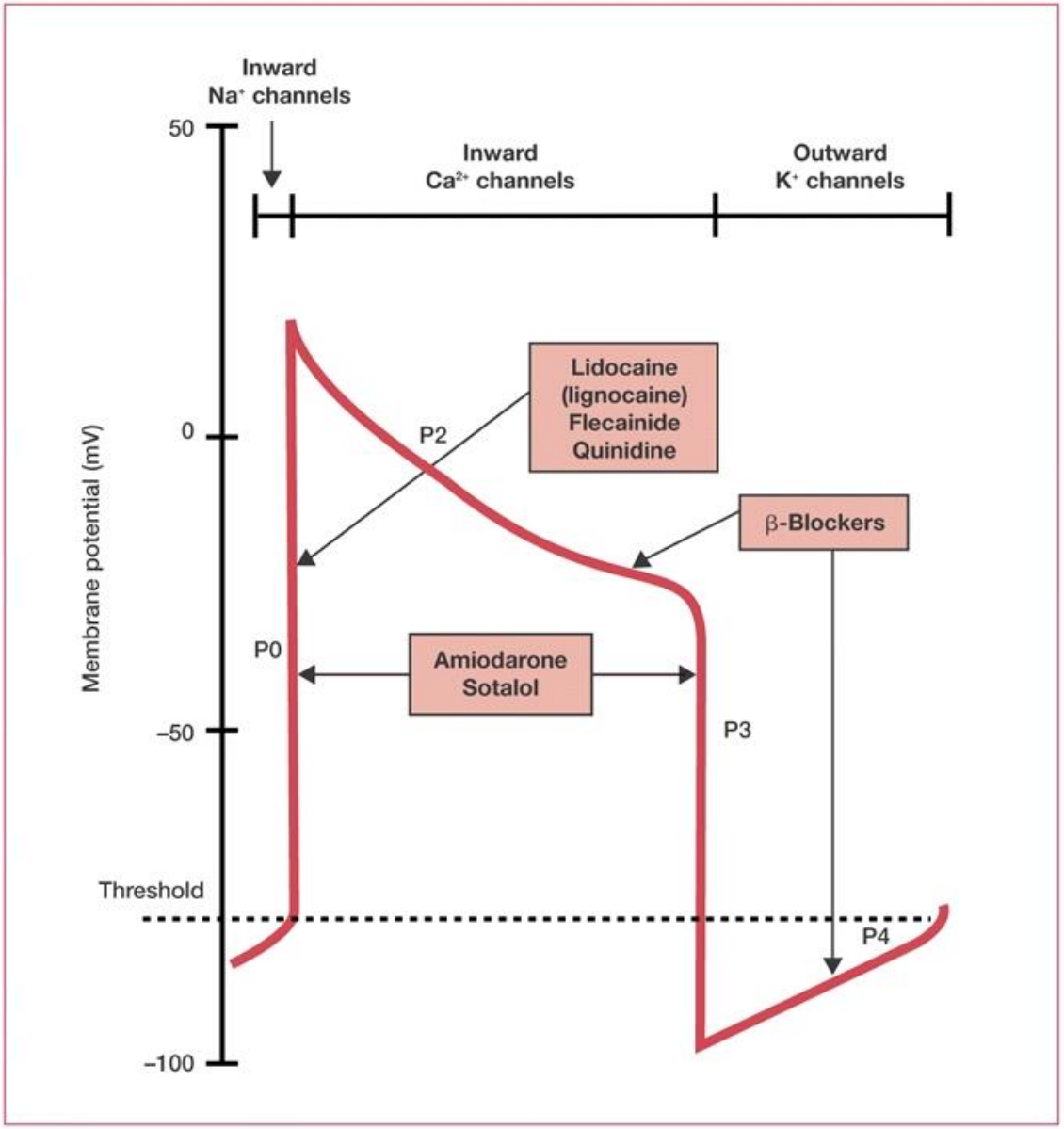
- alteration in the normal sequence of heart electrical impulse activation
- abnormality in the rate, site of origin or conduction pathway of the impulse
- bradycardia (<60 beats/min), tachycardia (>100 beats/min), flutter, fibrilation

Arrhythmias





Physiological contraction



Arrhythmia therapy

- Invazive: intracardial cardiostimulators, defibrilators
- Medication: **antiarrhythmics**

Antiarrhythmics

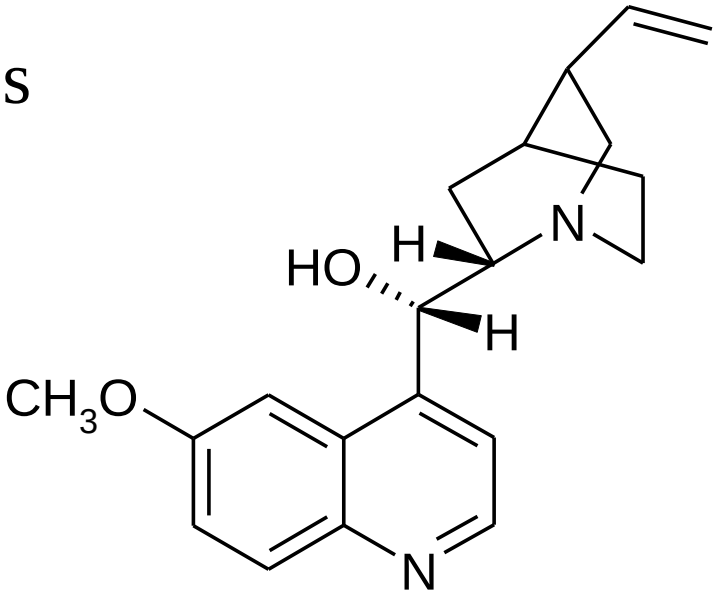
- The ultimate goal of antiarrhythmic drug therapy:
  - Restore normal sinus rhythm and conduction
  - Prevent more serious and possibly lethal arrhythmias from occurring.
- Antiarrhythmic drugs are used to:
  - ✓decrease conduction velocity
  - ✓change the duration of the effective refractory period (ERP)
  - ✓suppress abnormal automaticity

Antiarrhythmics: classification

class	mechanism	action	notes
I	Na^+ channel blocker	Change the slope of phase 0	Can abolish tachyarrhythmia caused by reentry circuit
II	β blocker	↓heart rate and conduction velocity	Can indirectly alter K and Ca conductance
III	K^+ channel blocker	1. ↑action potential duration (APD) or effective refractory period (ERP). 2. Delay repolarization.	Inhibit reentry tachycardia
IV	Ca^{++} channel blocker	Slowing the rate of rise in phase 4 of SA node(slide 12)	↓conduction velocity in SA and AV node

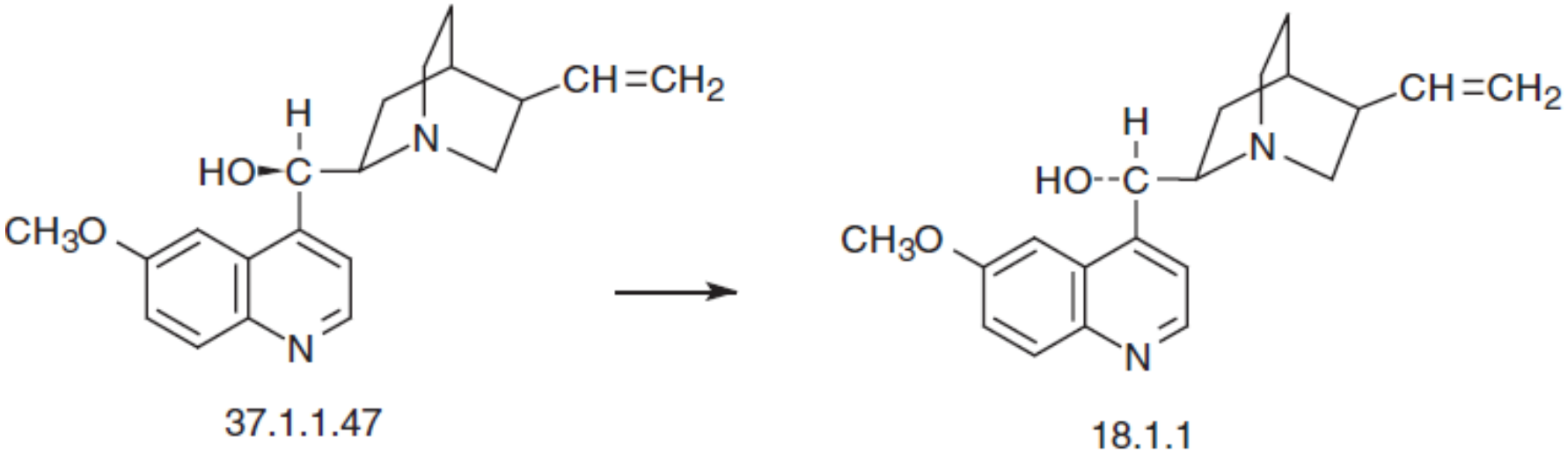
Class I A. Quinidine

- Alcaloid of cinchona bark
- isomer of quinine
- side effect – GIT disturbancies
- same effects as quinine –
- antimalaric, fever-reducing



Quinidine

Quinidine synthesis

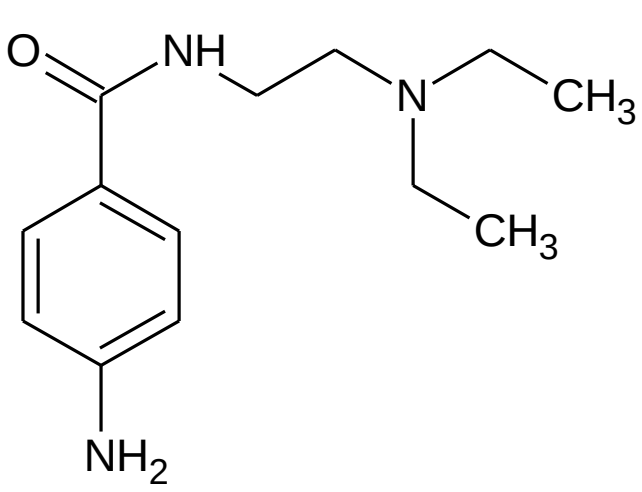


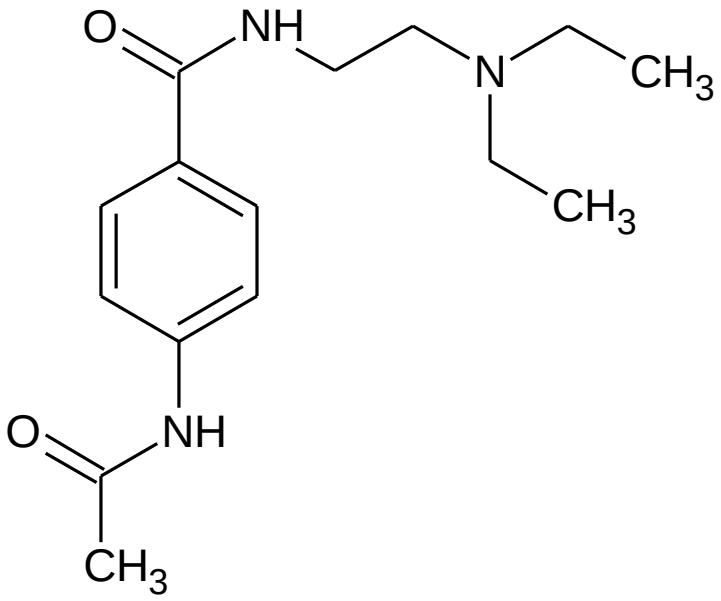
37.1.1.47

18.1.1

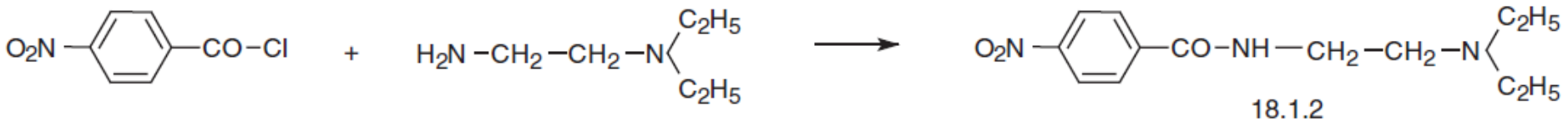
Class I A. Procainamide

N-acetylated metabolite is class III antiarrhythmic
long term administration: lupus erythromatosus





Procainamide synthesis



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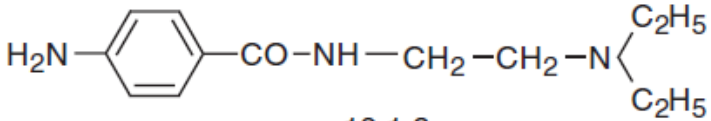
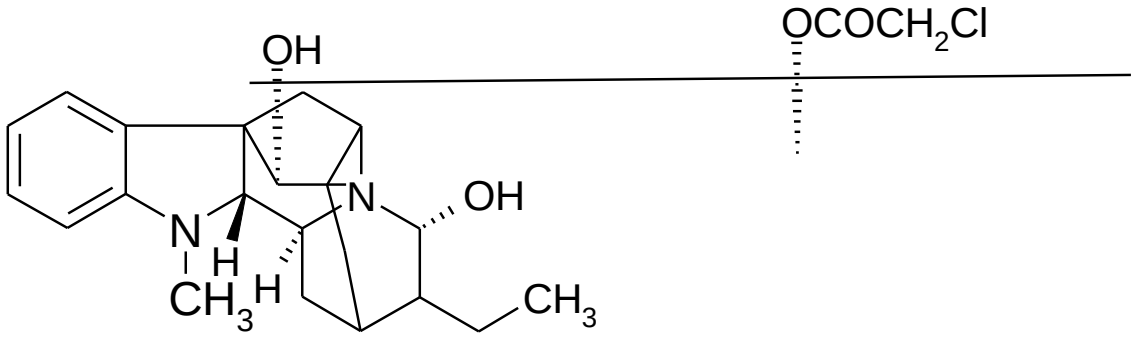


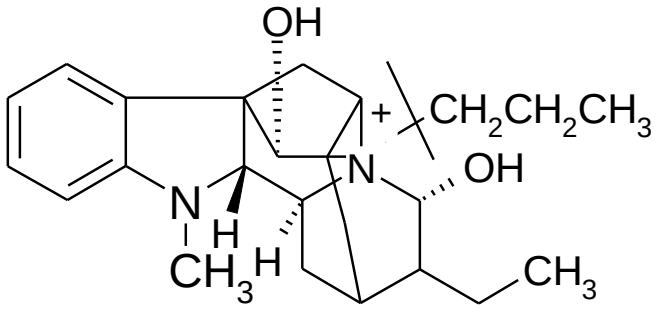
18.1.3

Class I A. Ajmaline, Prajmaline, Lorajmine

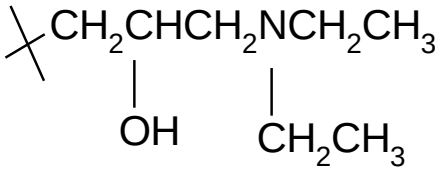


ajmalin

lorajmin



prajmalium

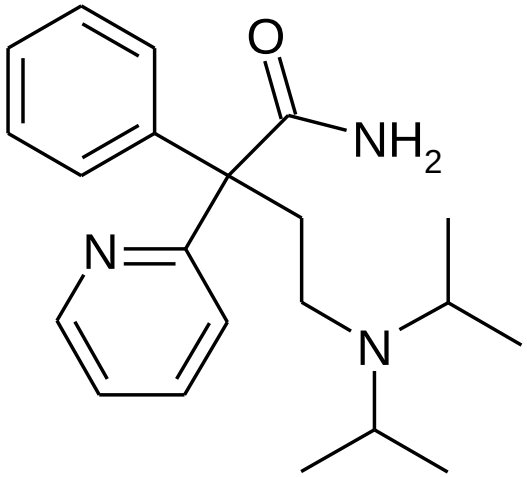


detajmium

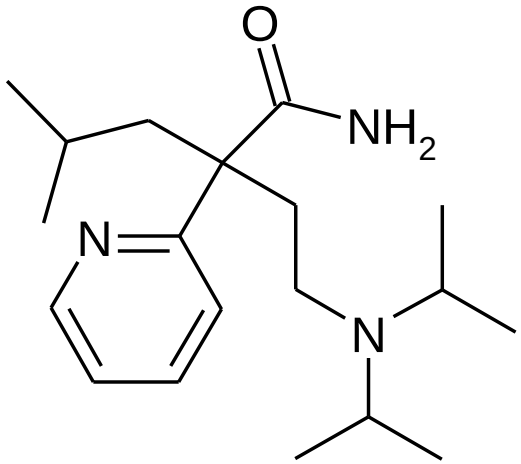
Class I A. Ajmaline, Prajmaline, Lorajmine

- Rauwolfia alcaloids
- semisynthetic derivatives have better bioavailability

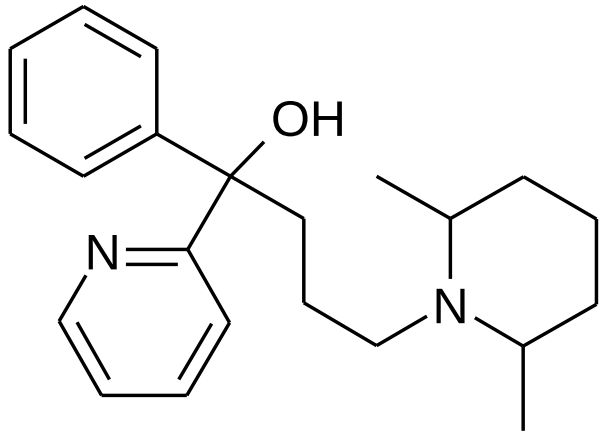
Class I A. Disopyramide, Pentisomide, Pirmenol



Disopyramide



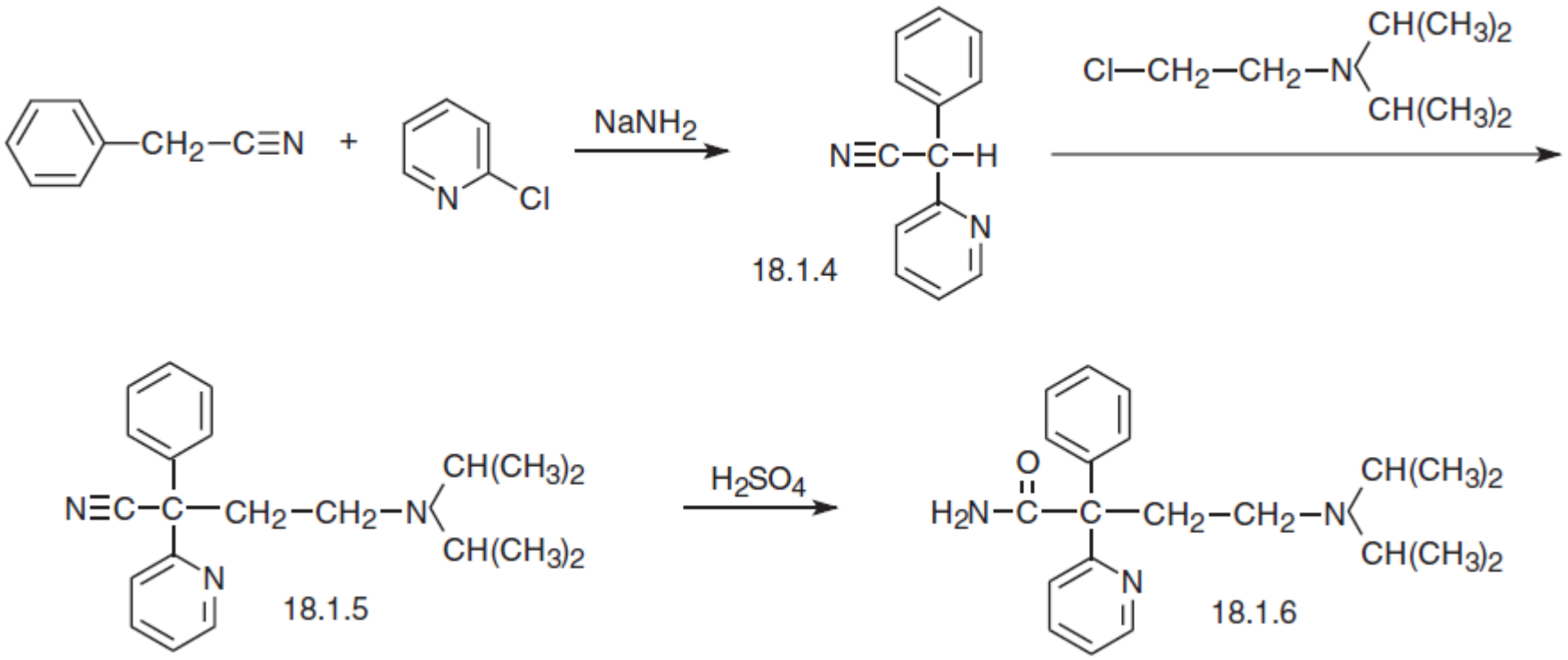
Pentisomide



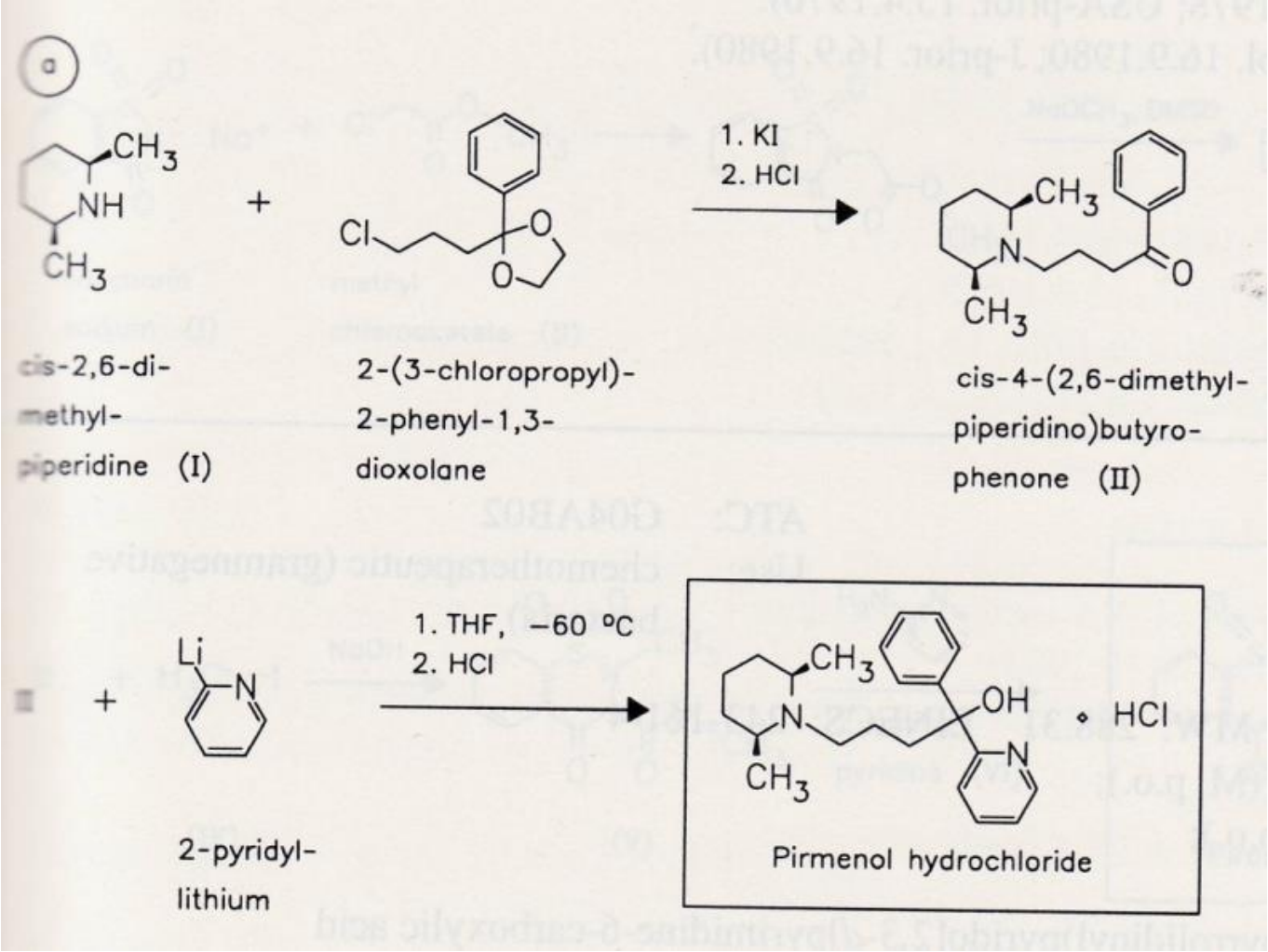
Pirmenol

pentisomide used only in Asia
side effect – cholinergic stimulation

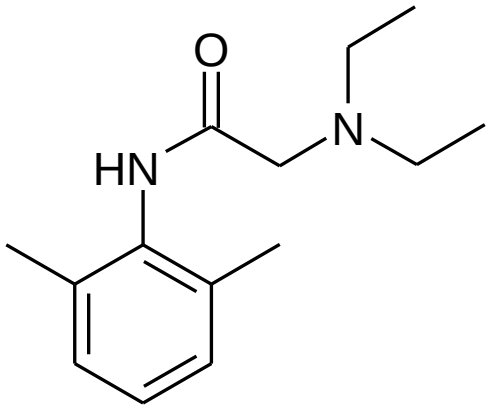
Disopyramide synthesis



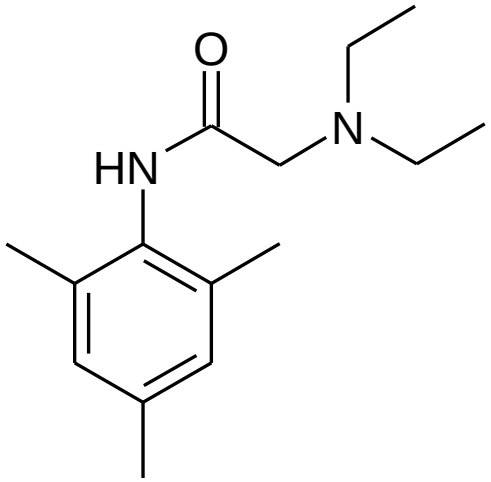
Pirmenole synthesis



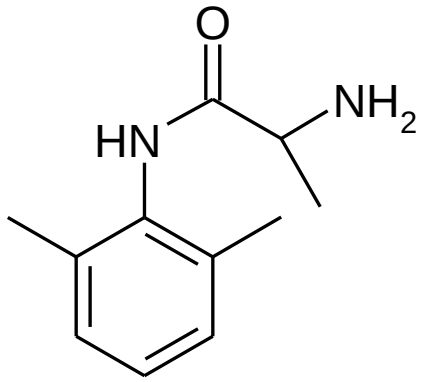
Class I B.



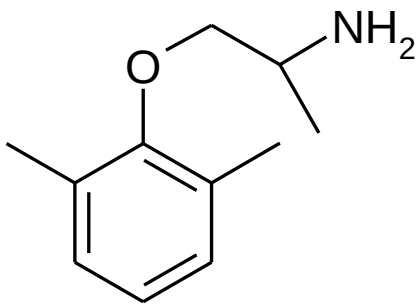
Lidocain



Trimecain

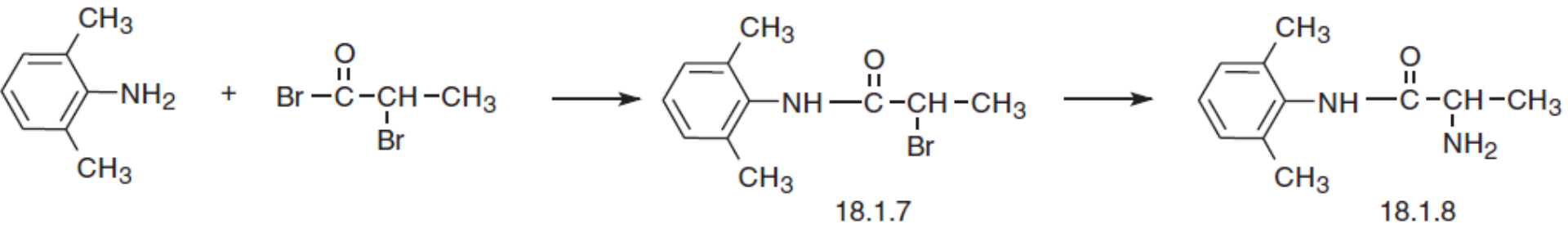


Tocainide

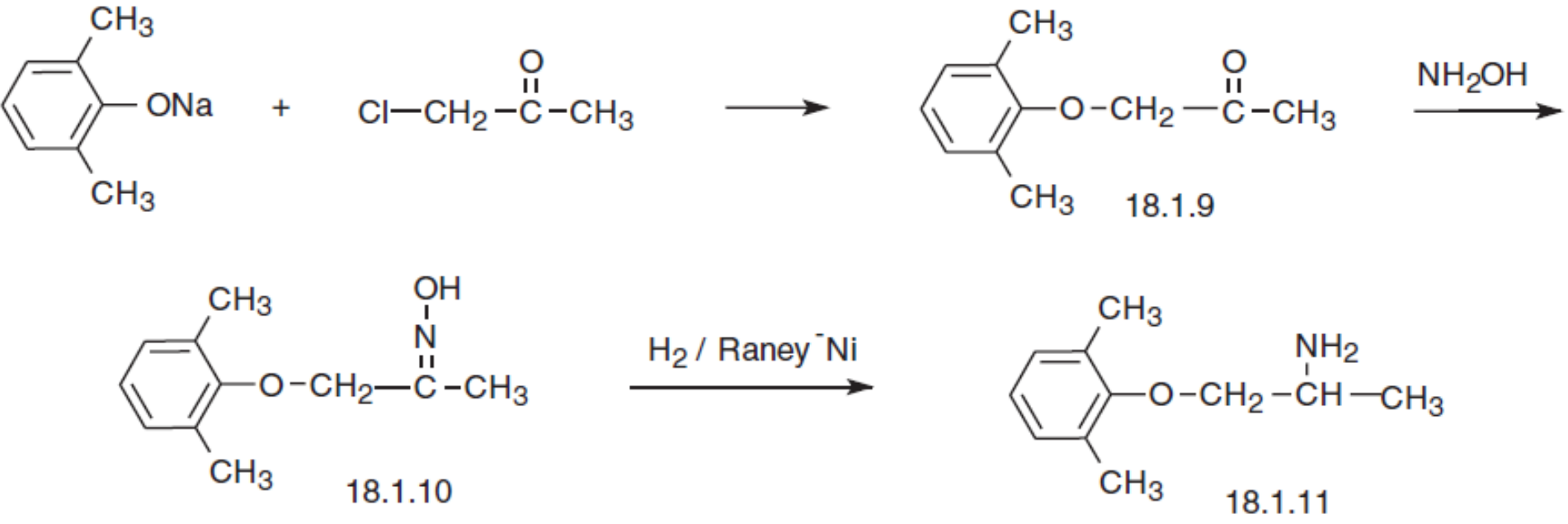


Mexilethine

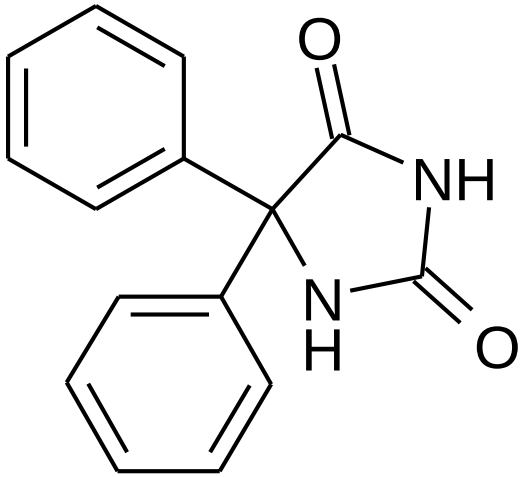
Tocainide synthesis



Mexilethine synthesis



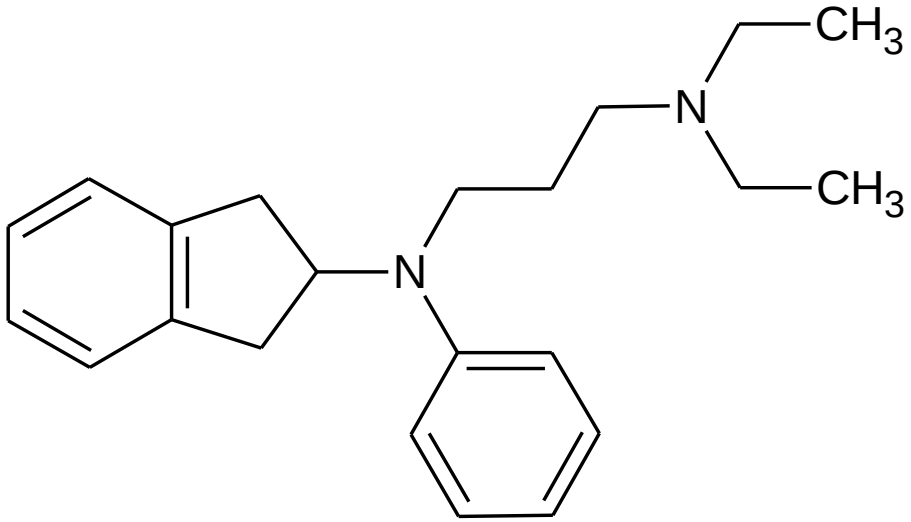
Class I B.



Phenytoin

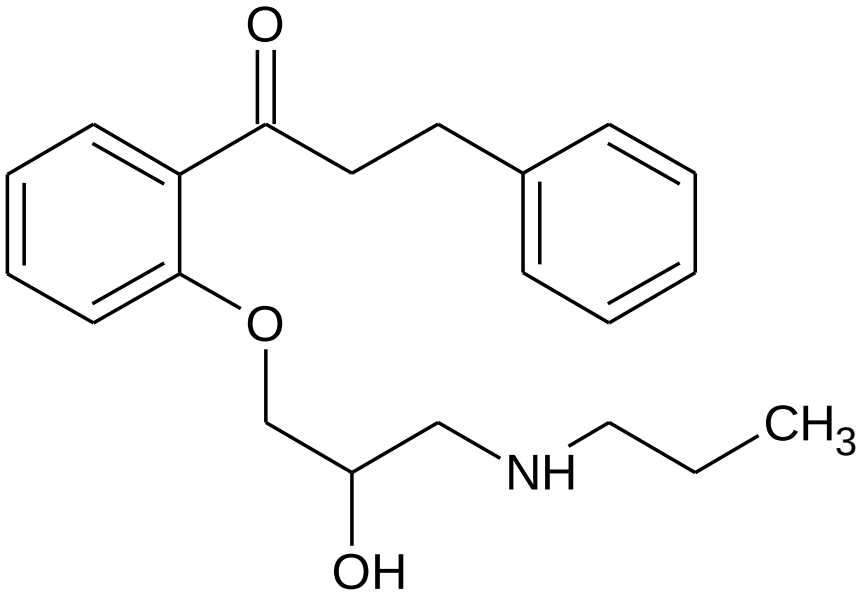
antiepileptic drug with antiarrhythmic effect
peroral use, limited use
antitoxine in digitalis intoxication

Class I B.



Aprindine
used in Japan

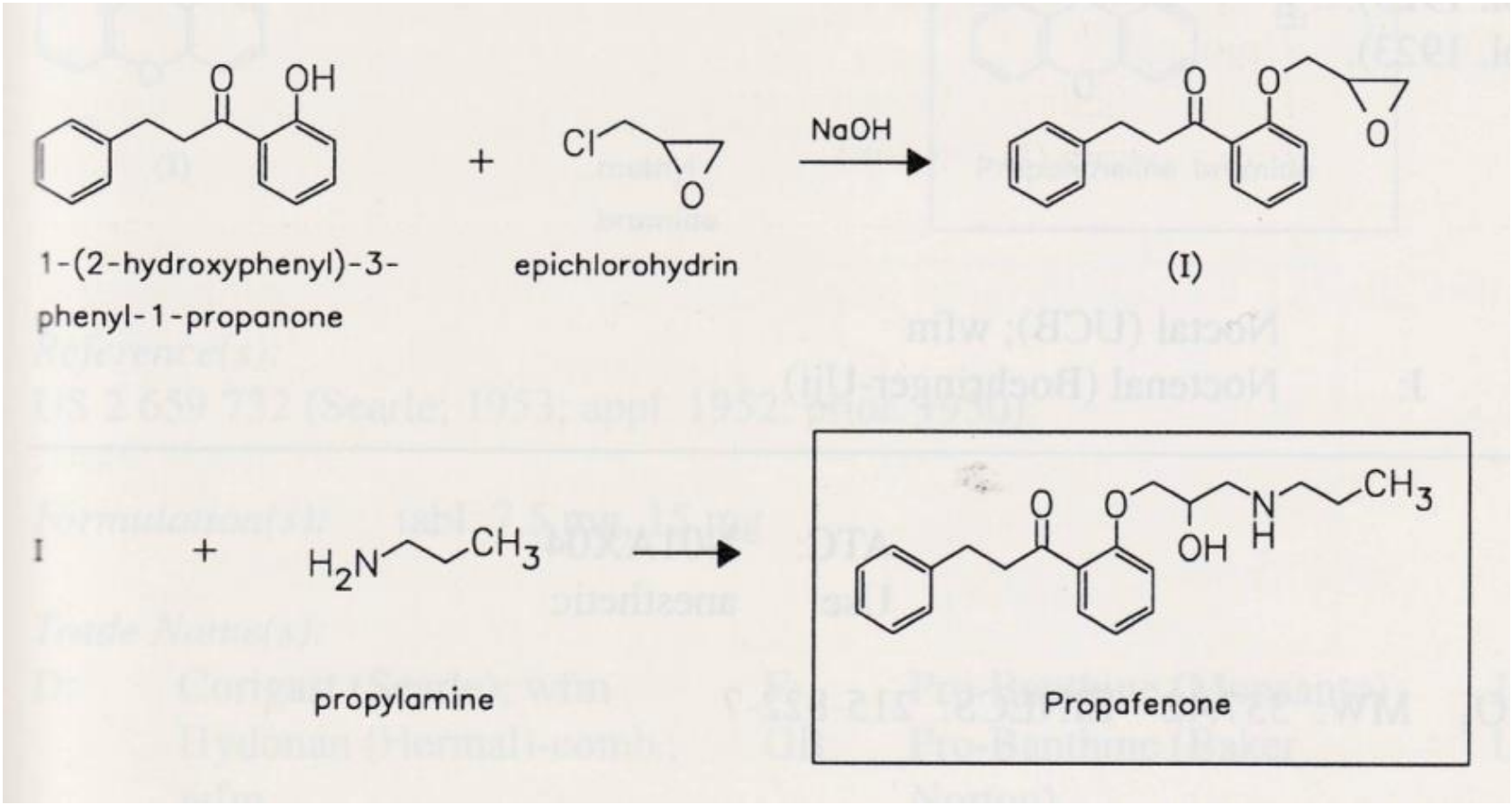
Class I C.



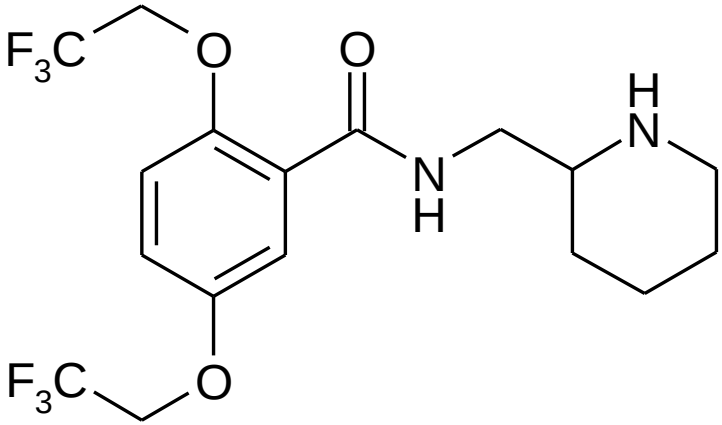
propafenone

short biological half-time, 3x a day administration

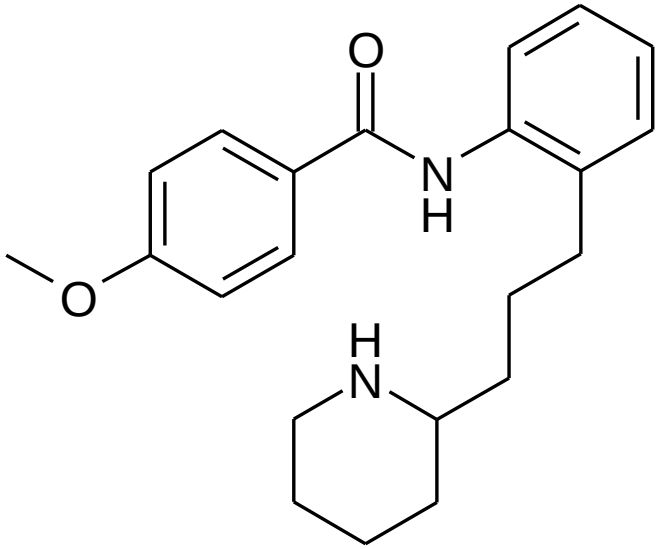
Propafenone synthesis



Class I C.



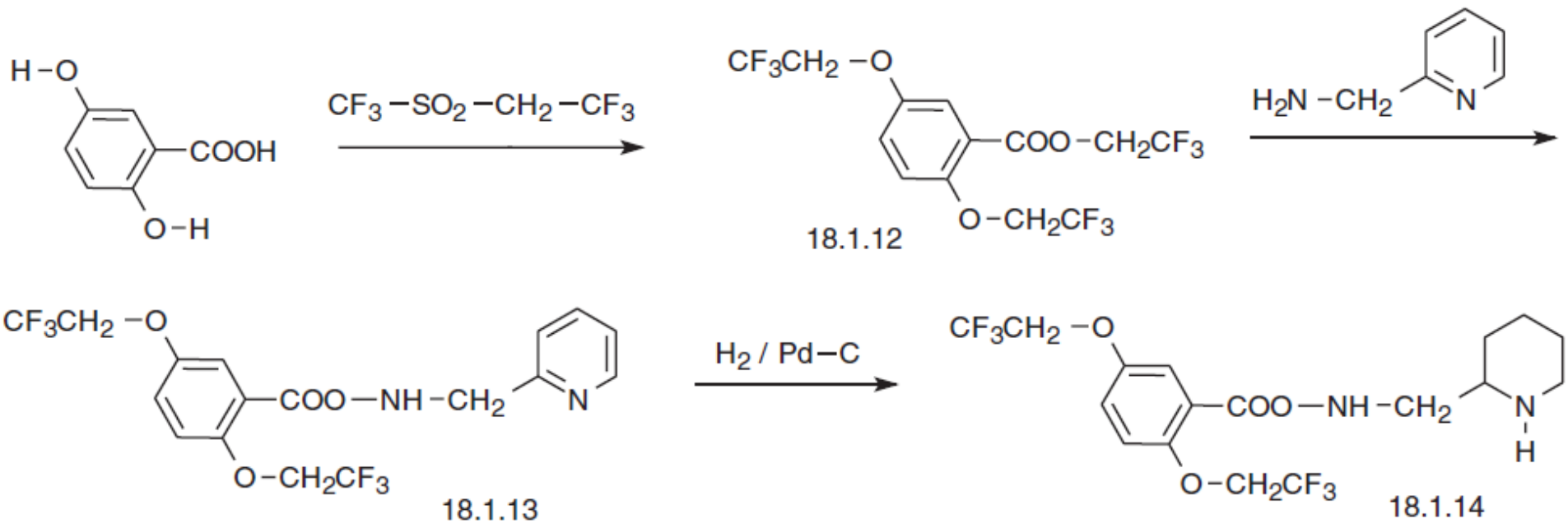
Flecainide



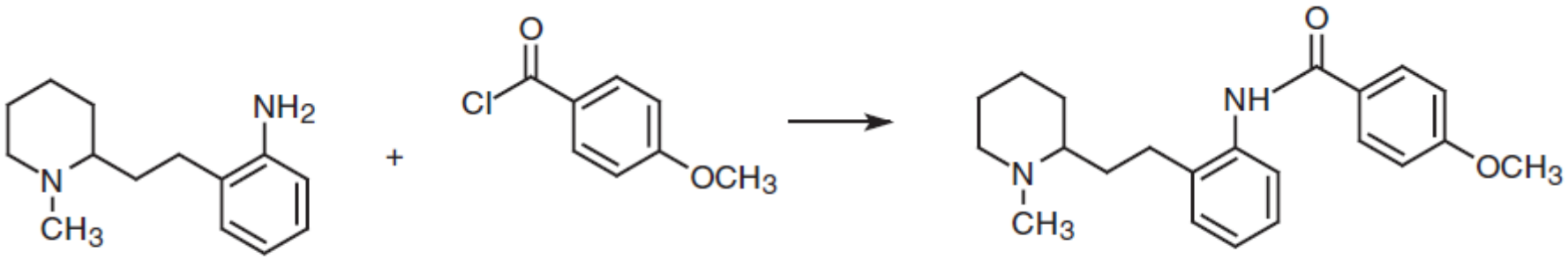
Encainide

risk of cardiotoxicity, controlled use.
encainide withdrawn in 1991 in US

Flecainide synthesis

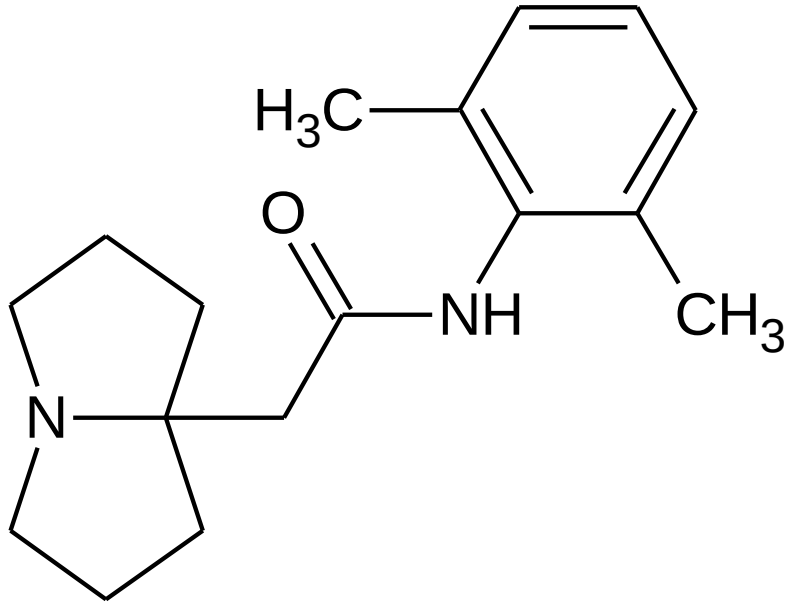


Encainide synthesis



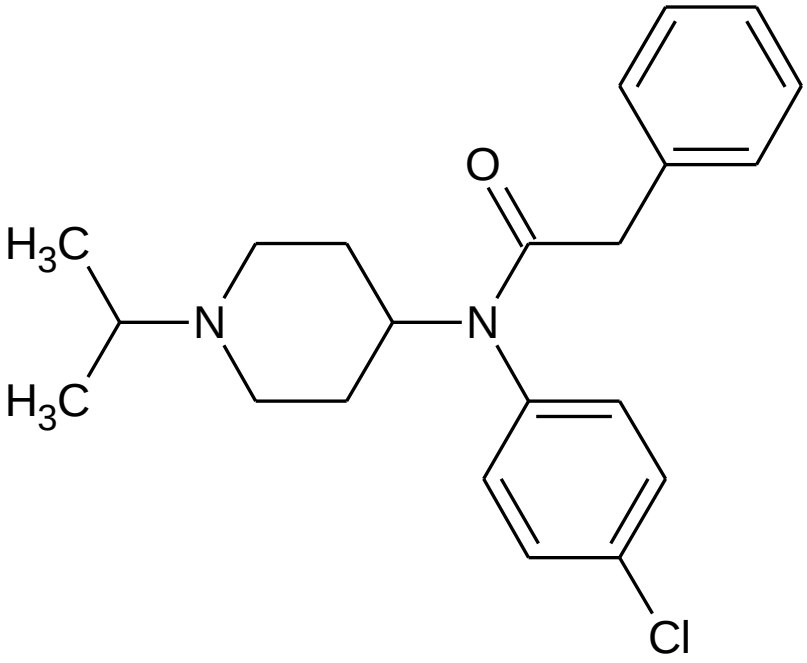
18.1.15

Class I C.



pilsicainide
marketed in Japan

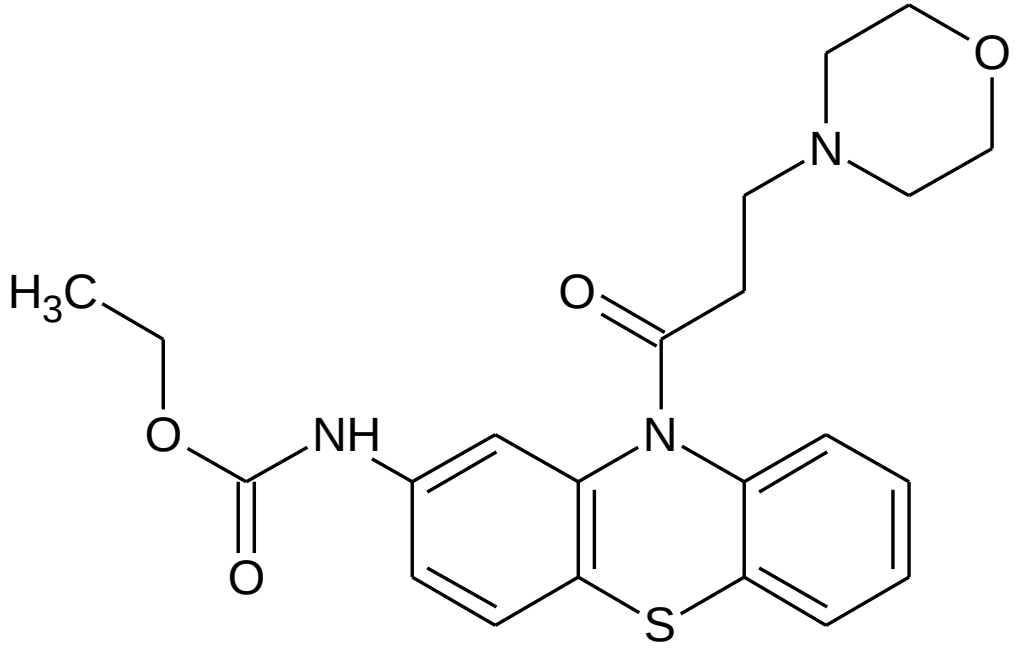
Class I C.



lorcainide

good safety profile, perorally available, prolonged duration of action (8-10 hrs)

Class I C.

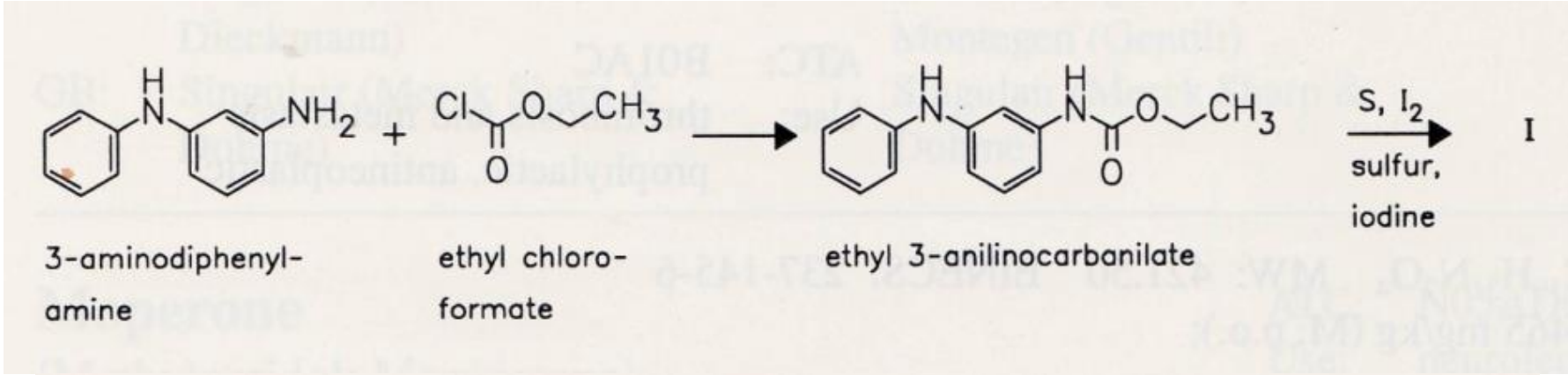


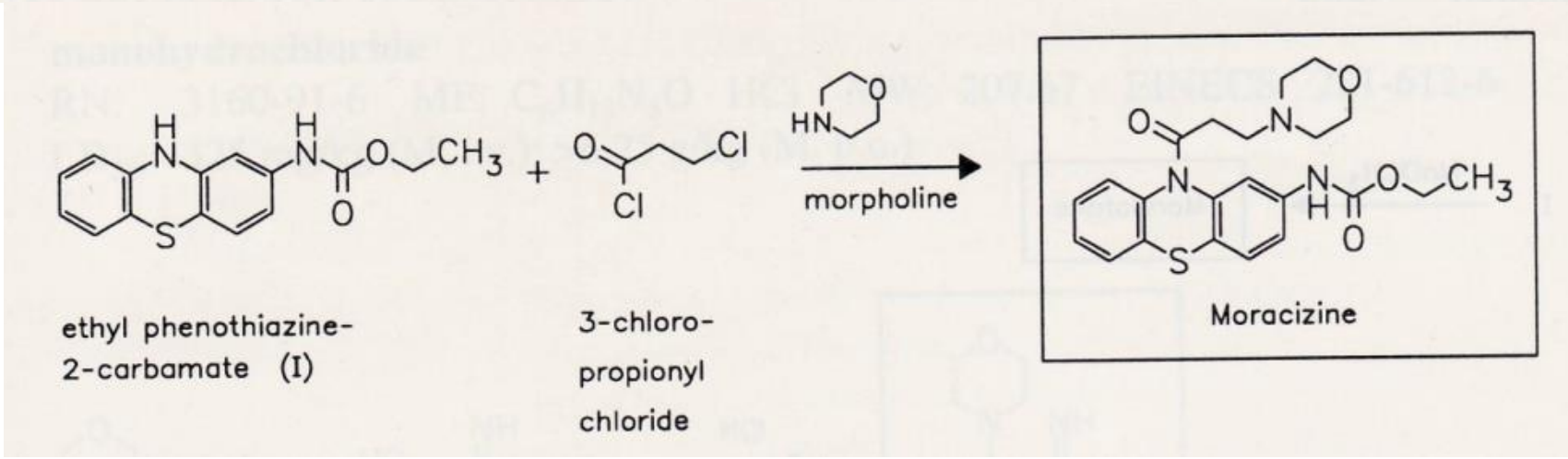
Moracizine (moricizine)

peroral administration, short biological half-time (3 hrs)

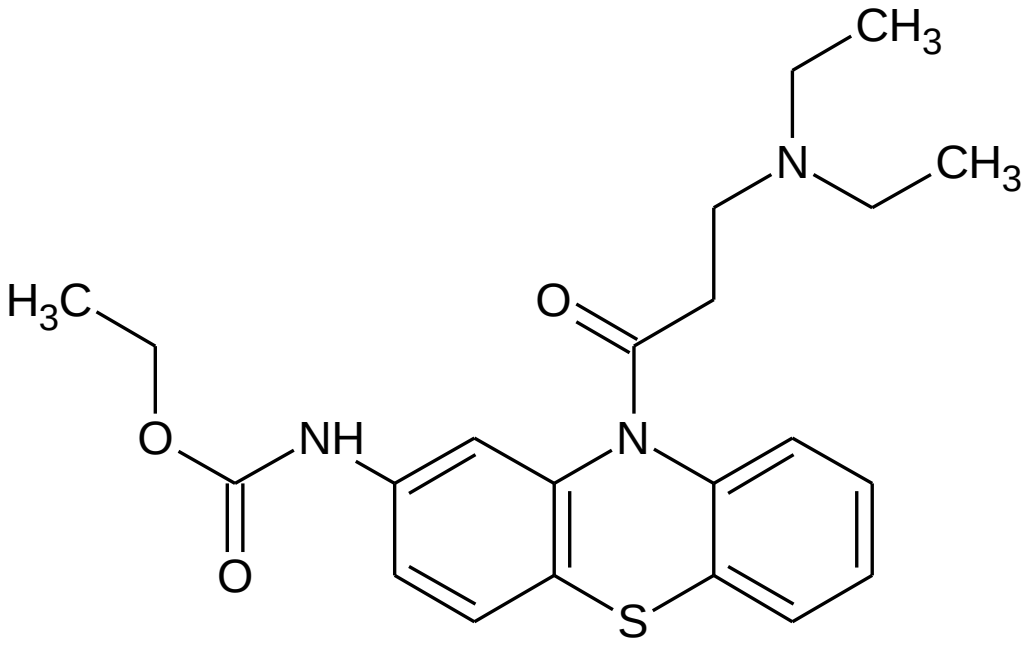
discontinued in 2007 due to economical reasons

Moricizine synthesis





Class I C.



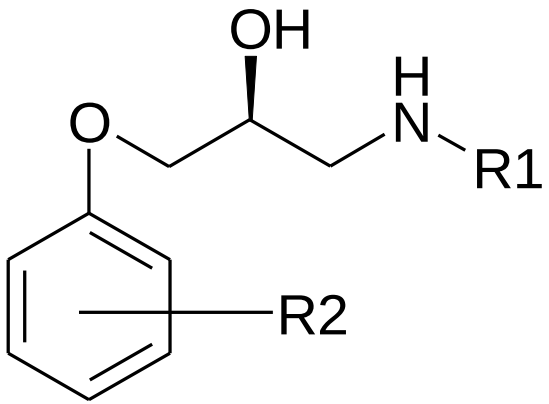
Ethacizine (Ethacyzine)

derivative of moracizine with almost same properties marketed in Russia and east-Europian countries

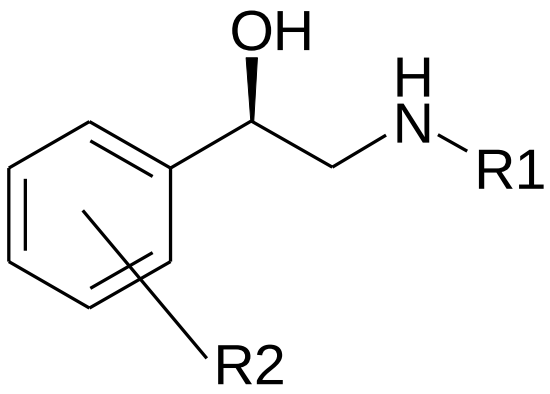
Class II.

- β-adrenergic receptor antagonists, used as antihypertensives; *see lecture Antiadrenergics*
- as antiarrhythmics used mainly: atenolol, acebutolol, bisoprolol, metipranolol, metoprolol, pindolol, oxprenolol, karteolol, penbutolol, talindolol, esmolol (ultra-short action), nadoxolol, propranolol

Class II.



Aryloxypropanolamines



Arylethanolamines

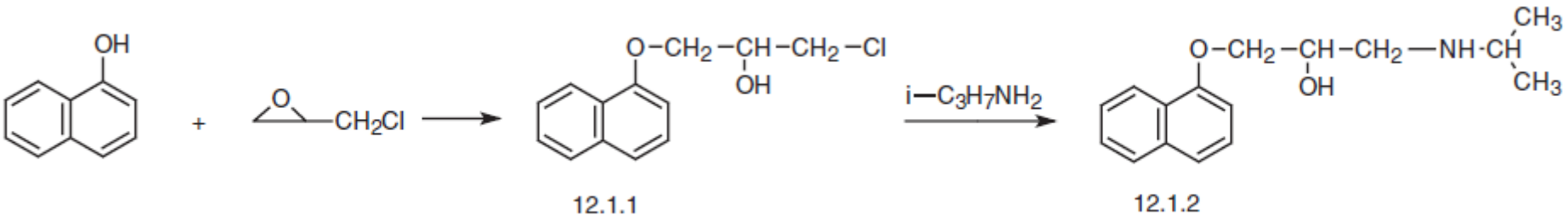
R1: isopropyl-, isobutyl- or arylalkyl-

R2: various substituents

o-substitution or another ring = non-selective

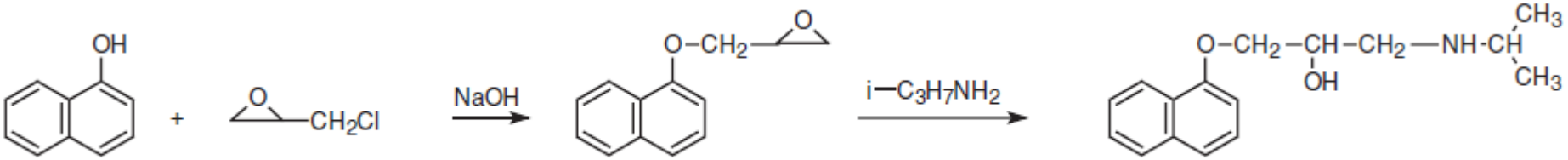
p-substitution = cardioselectivity (β_1 selectivity)

example of synthesis



12.1.1

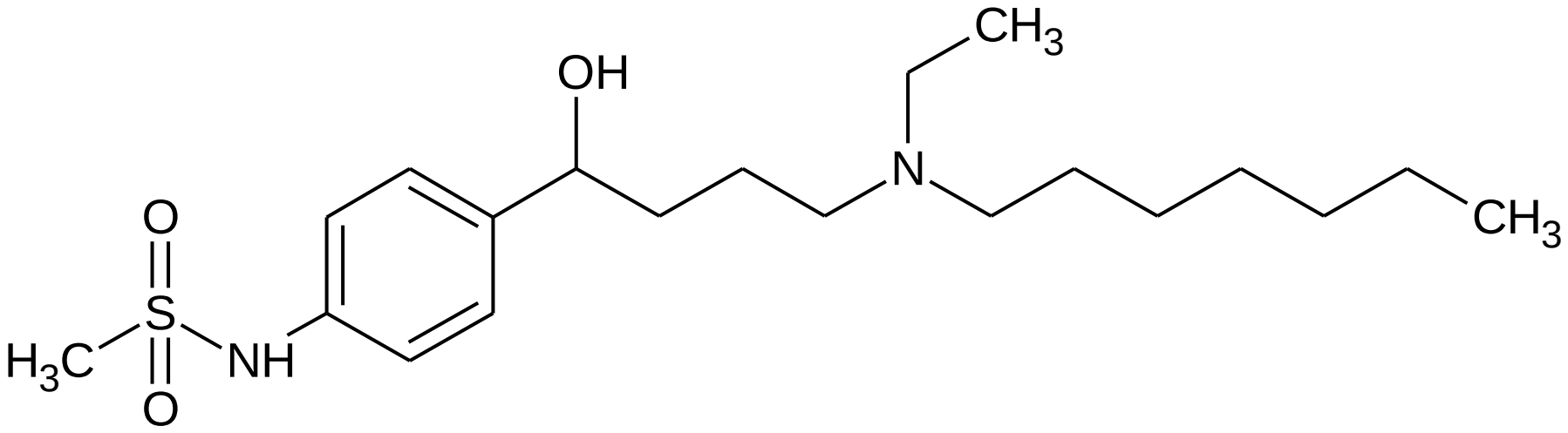
12.1.2



12.1.3

12.1.2

Class III.

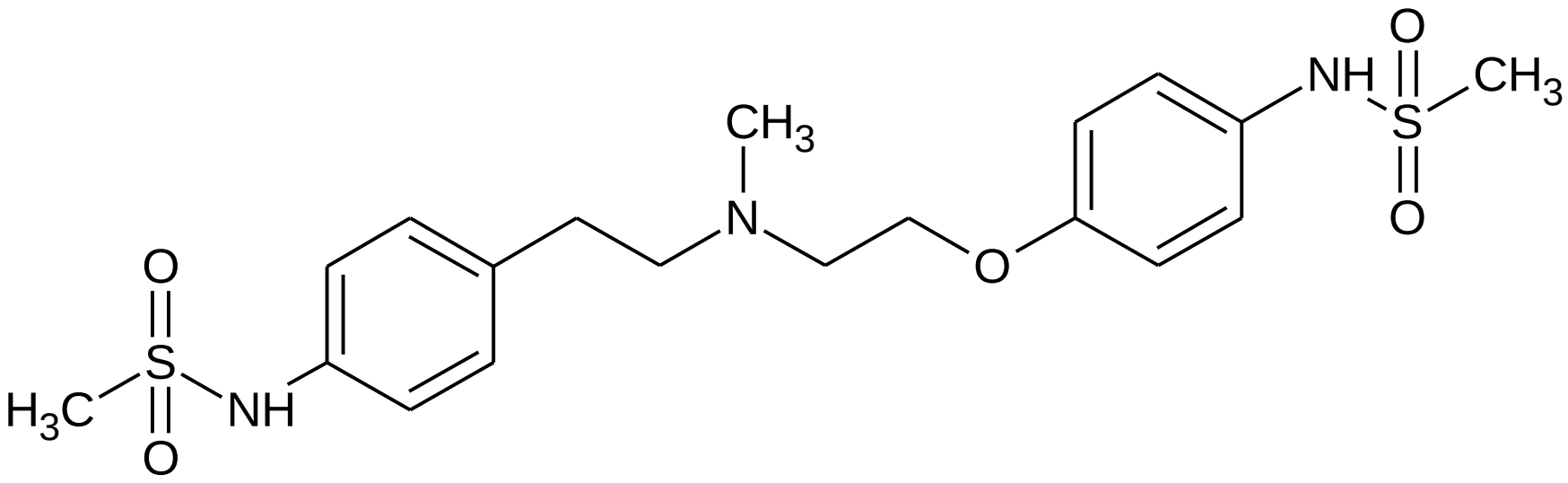


Ibutilide

i.v. administration, EKG monitoring during therapy

additional Ia class sodium channel effect

Class III.

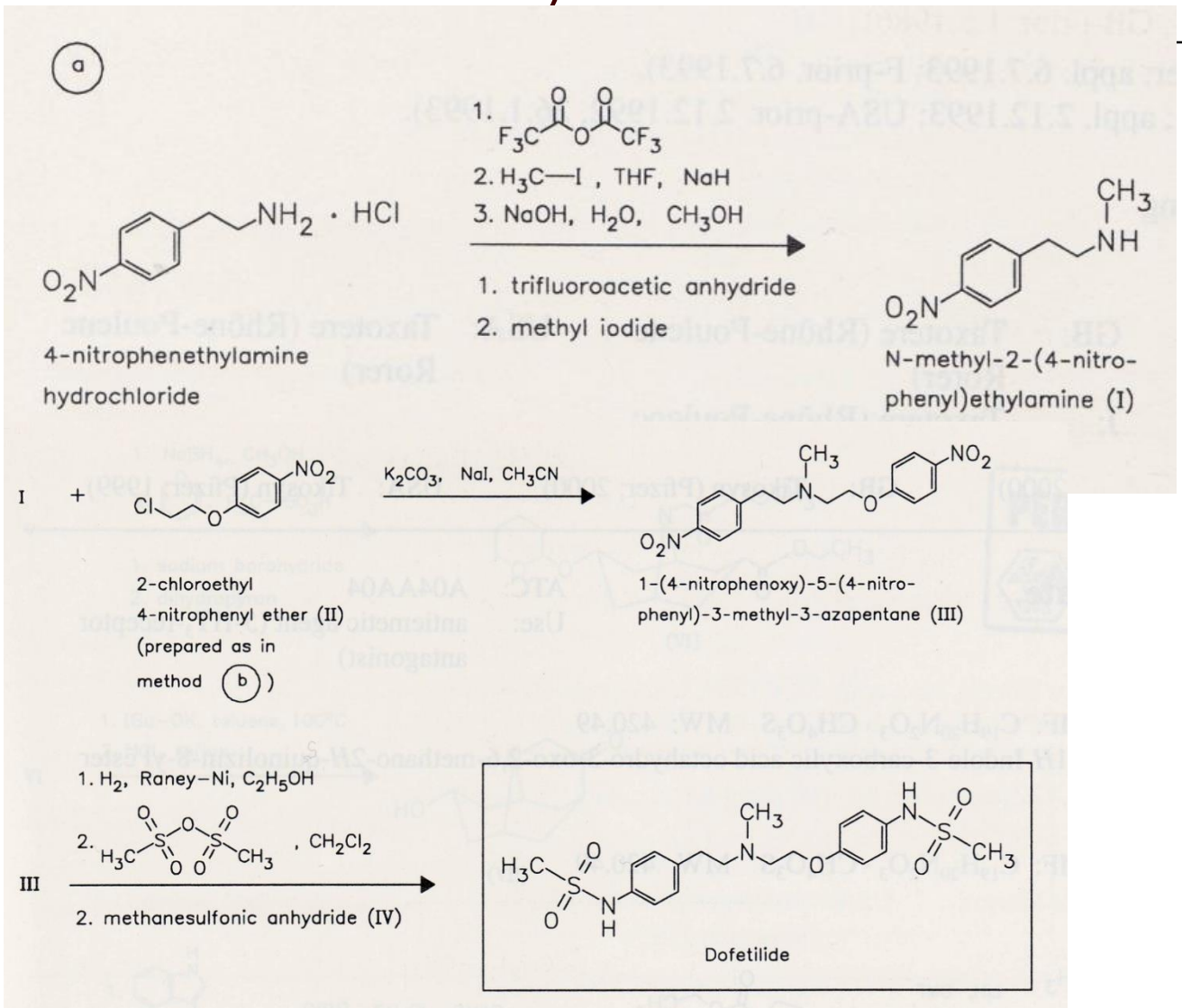


Dofetilide

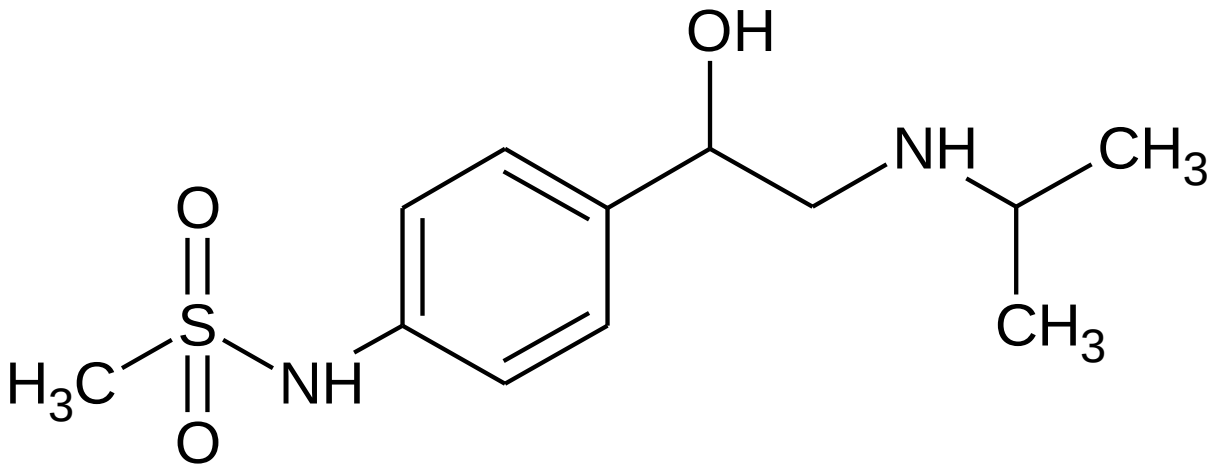
i.v. administration, EKG monitoring during therapy

additional Ia class sodium channel effect

Dofetilide synthesis



Class III.

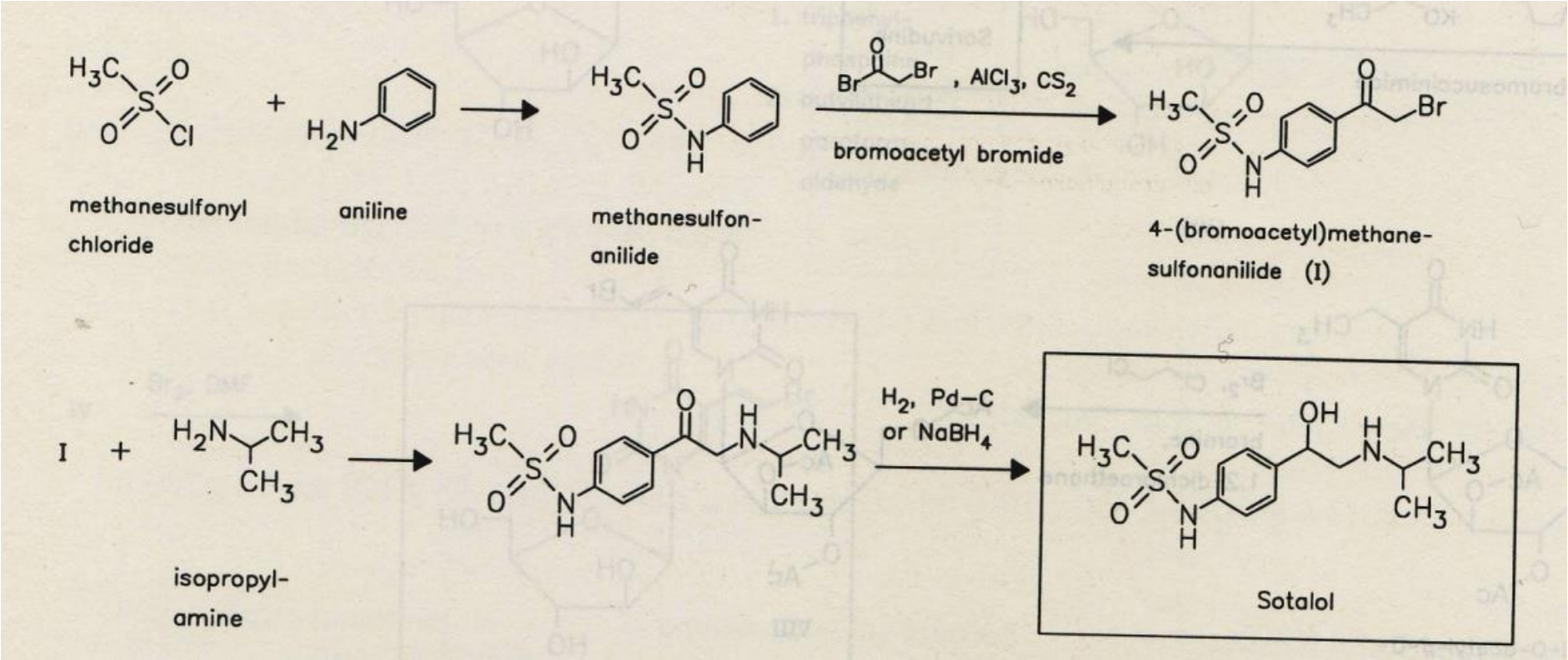


Sotalol

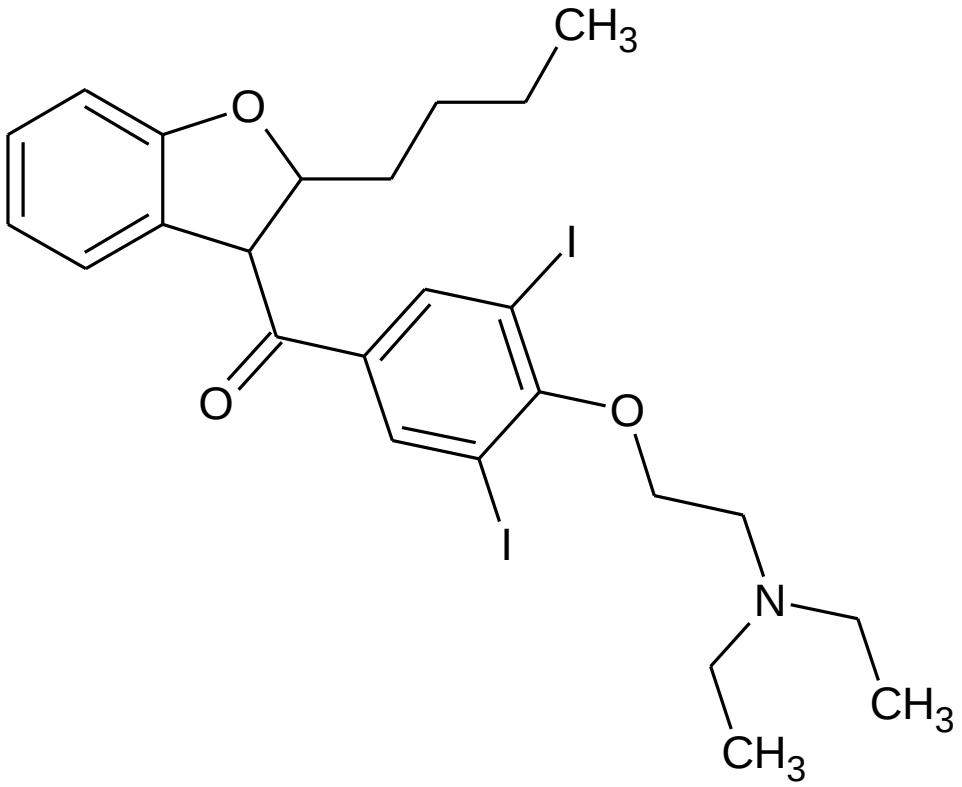
peroral administration, risk of life-threatening torsade de pointes tachycardia – used only in the case of serious arrhythmias

additional non-selective betablocking activity

Sotalol synthesis



Class III.



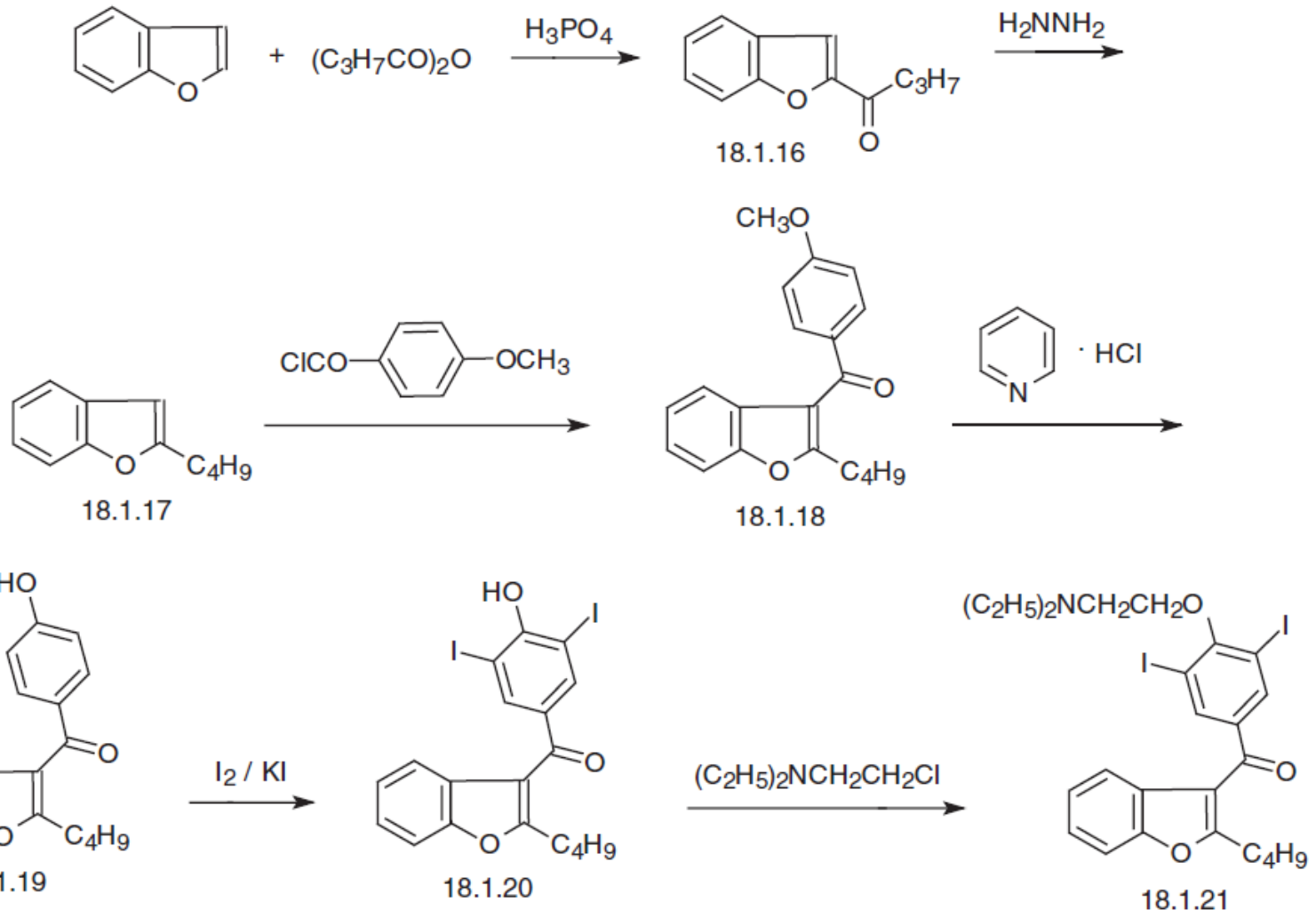
Amiodarone

serious toxicity, risk-to-benefit ratio should be considered

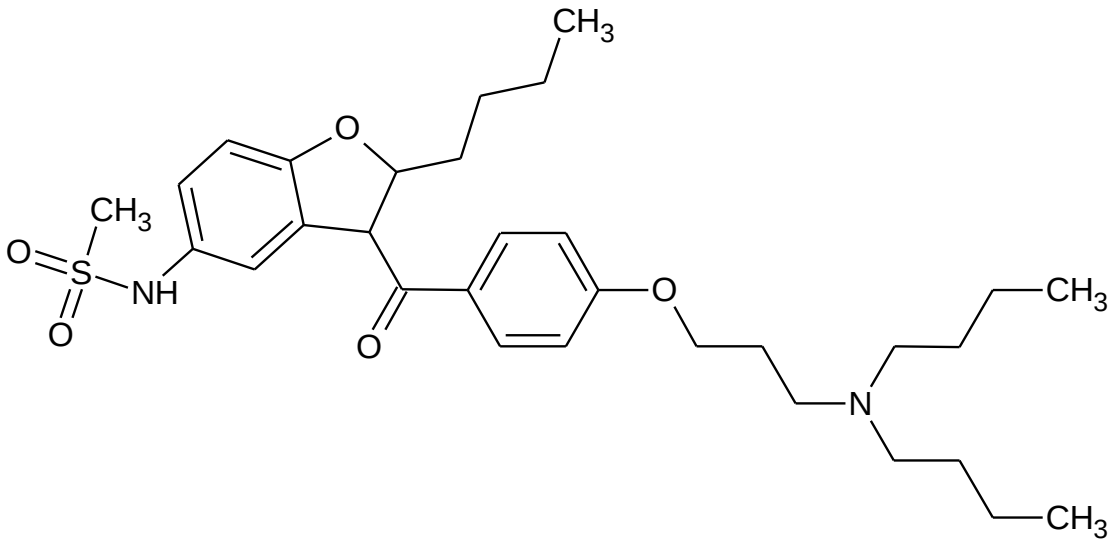
peroral or i.v. administration

additional betablocking, Ca^{2+} and Na^{+} ch. blocking activity

Amiodarone synthesis



Class III.



Dronedarone

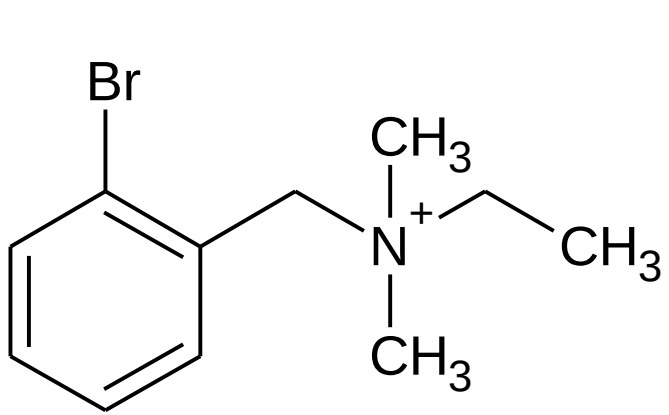
rapidly lower toxicity compared to amiodarone

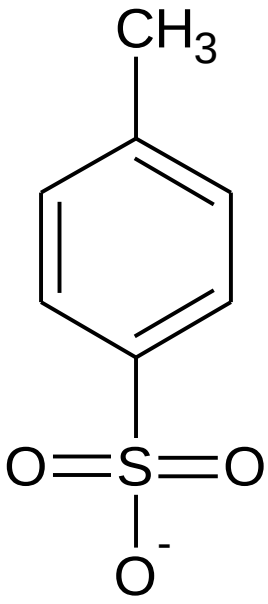
peroral administration

amiodarone-like effect

marketed since 2009

Class III.





Bretylium tosylate

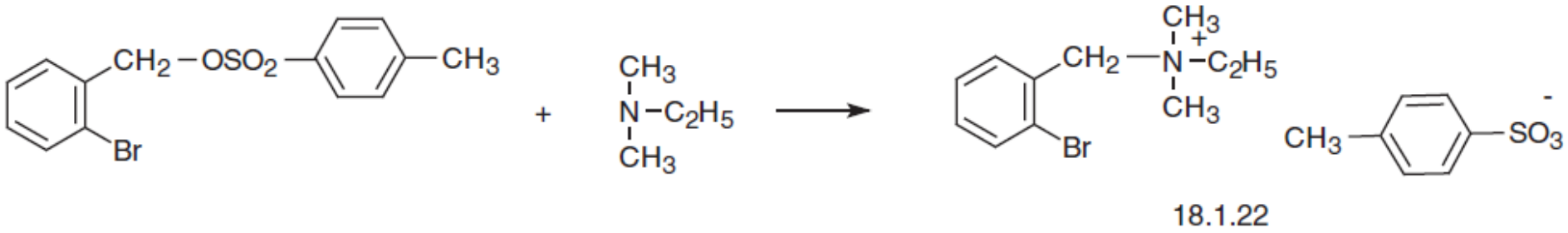
peroral administration

side effects – blood pressure disturbancies

hospitalization necessary when administered

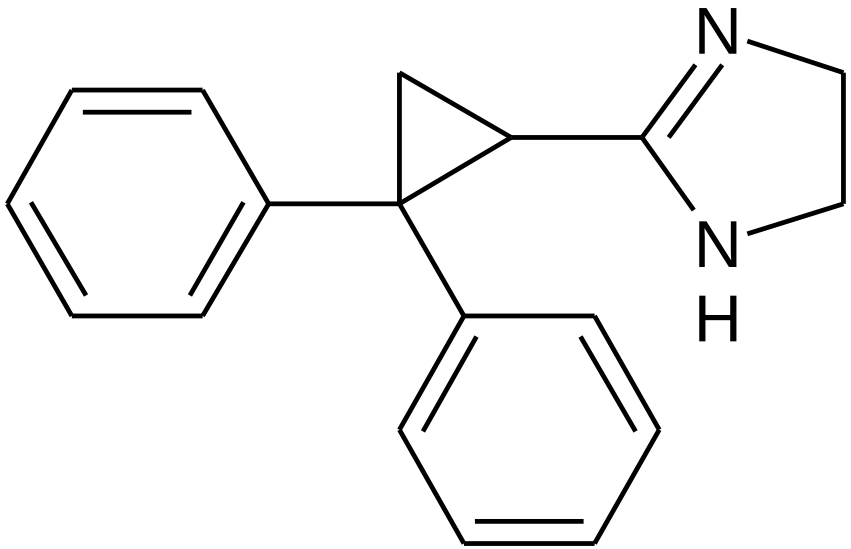
unavailable in most countries

Bretylium tosylate synthesis



18.1.22

Class III.



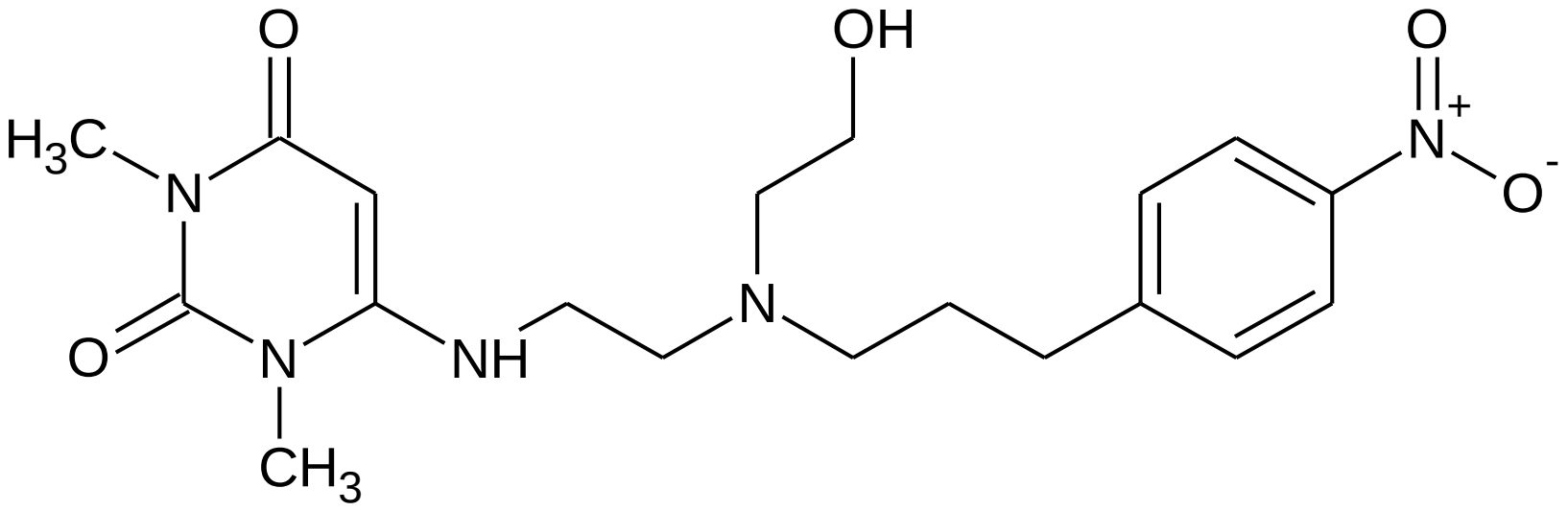
Cibenzoline

combined Ia and III class effects

marketed in Japan

weak cholinergic side effects

Class III.

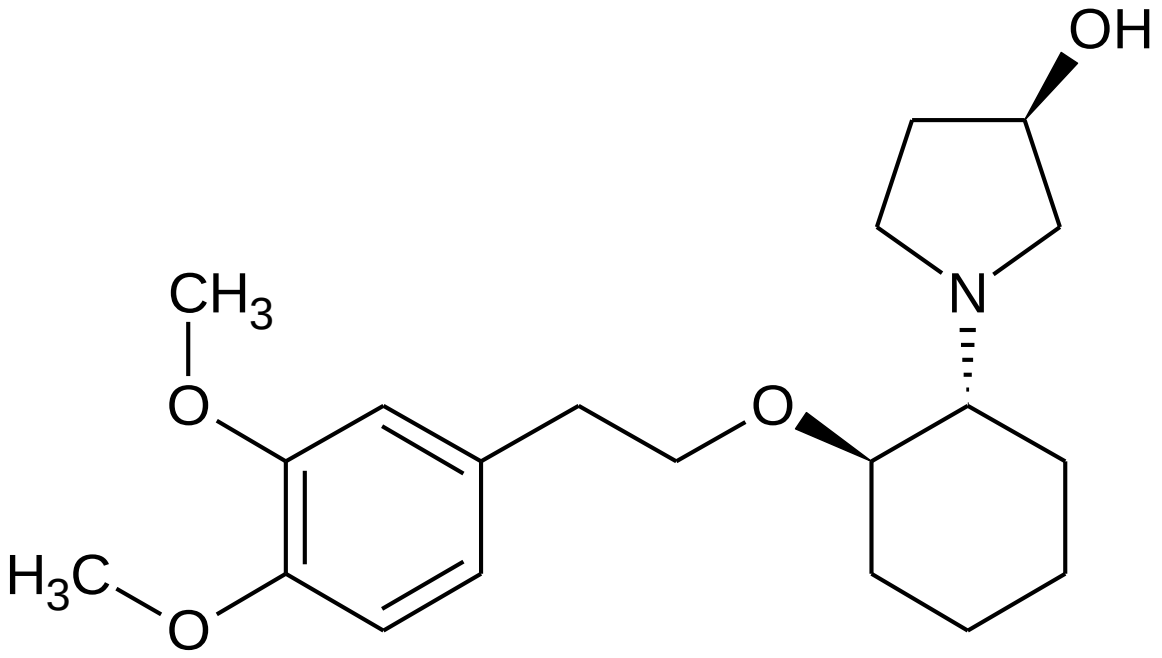


Nifekalant

marketed in Japan

better profile to other III class antiarrhythmics

Class III.



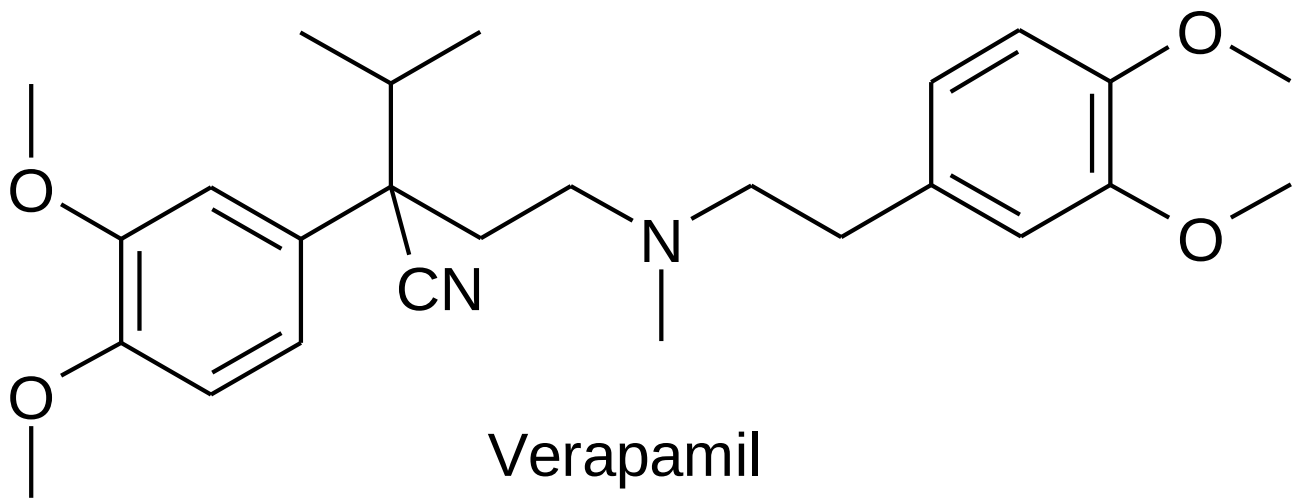
Vernakalant

more effective in higher heart rates compared to other antiarrhythmics

marketed in Europe

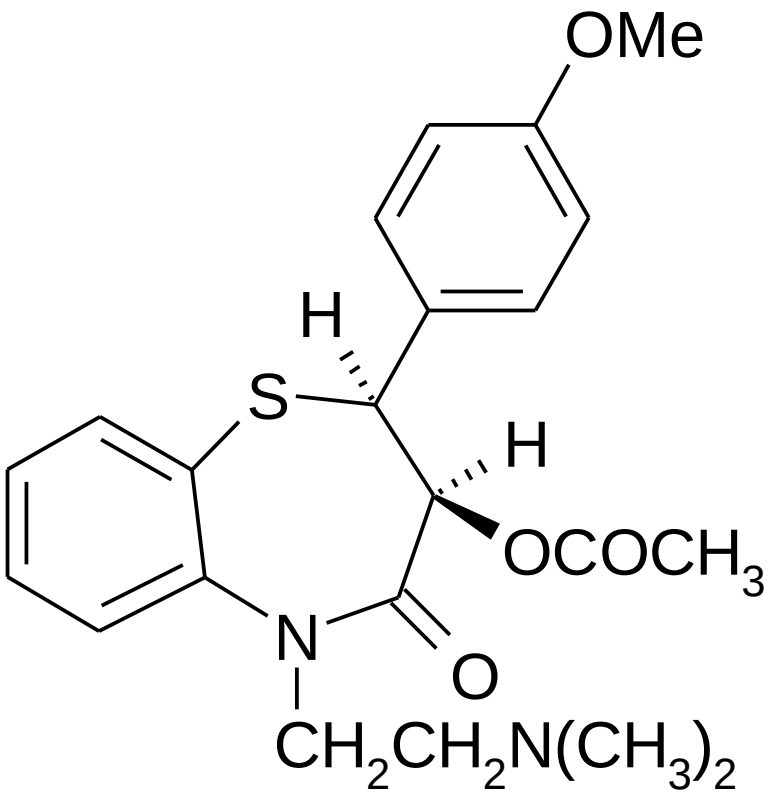
Class IV.

- Ca^{2+} channel blockers



Verapamil

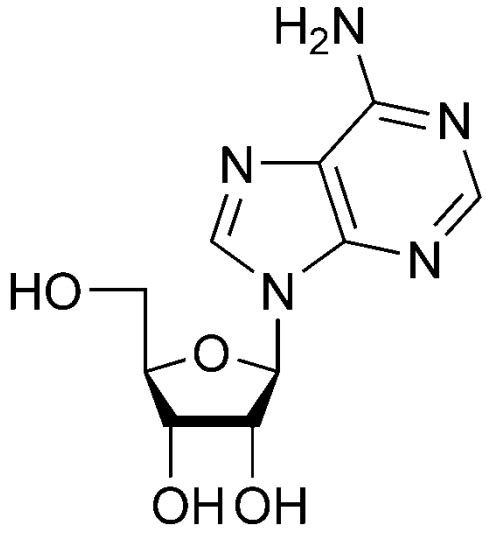
Class IV.



diltiazem

Drugs within classification

- digoxin – *see cardiotonics*
- adenosine



- both prolongs duration of action potential