Antiarrhythmics

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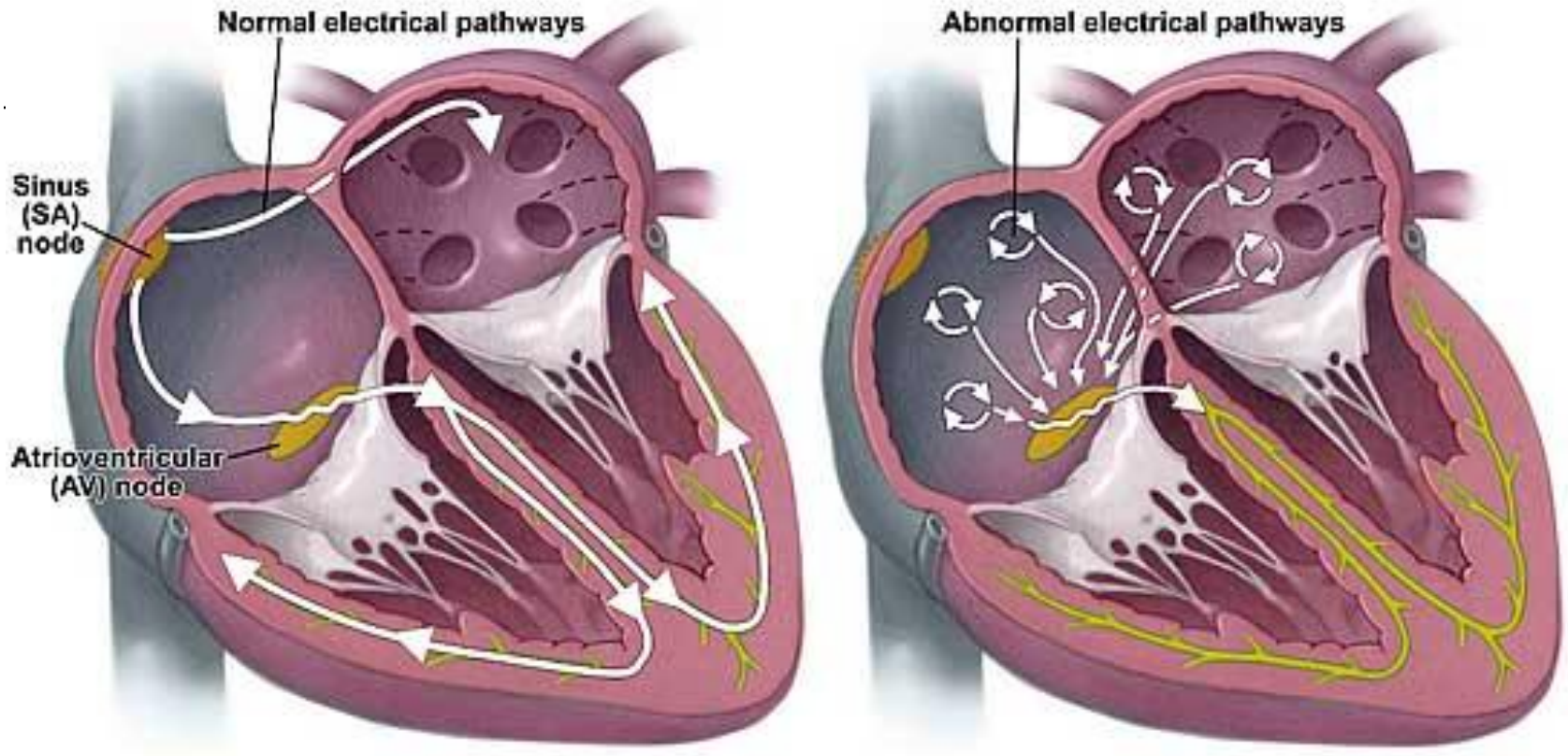
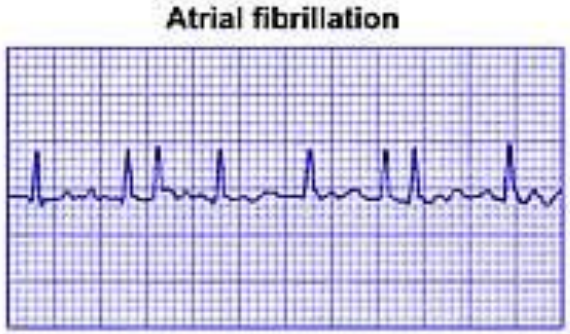
19.11.2012

Arrhythmia

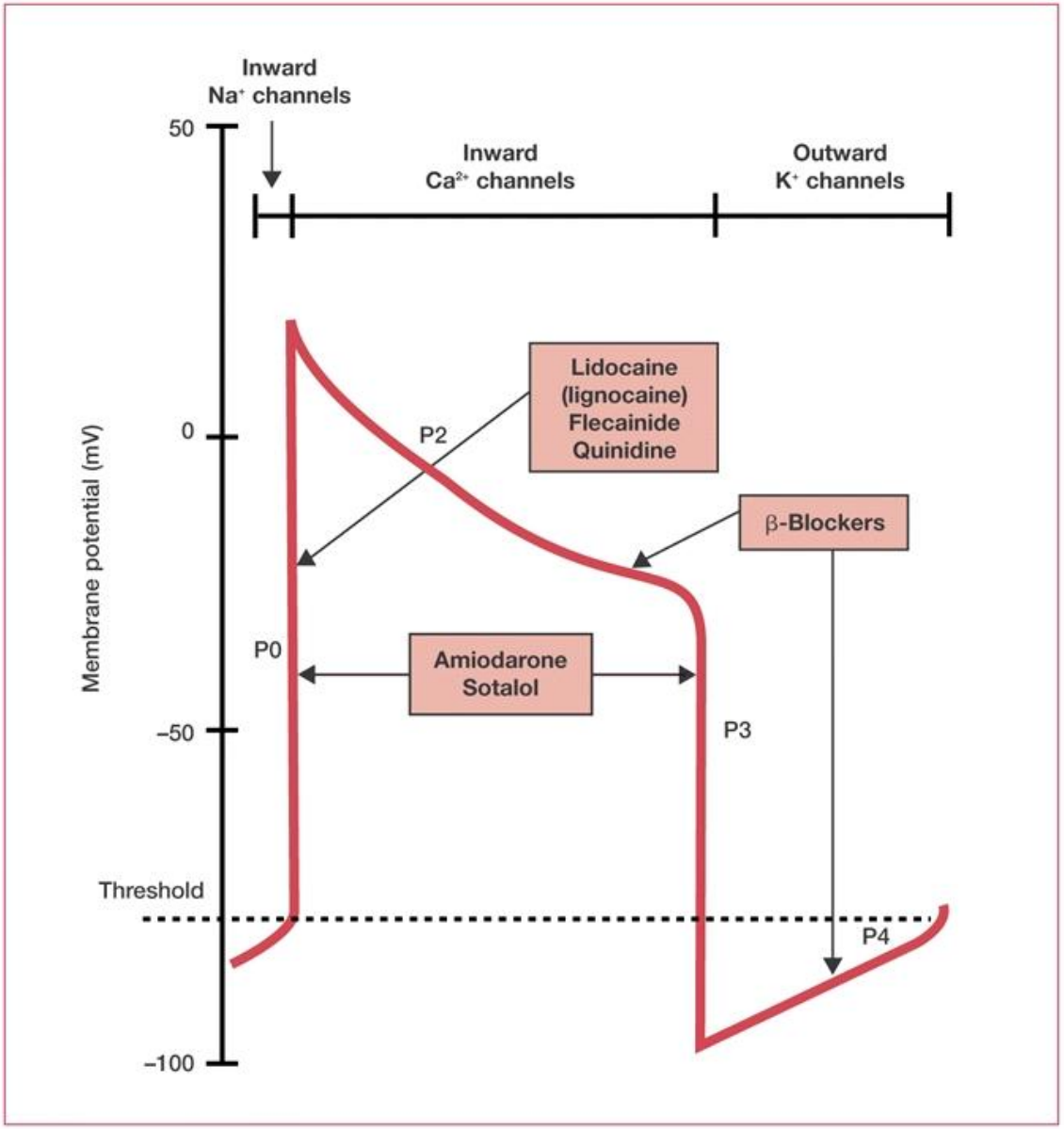
- alteration in the normal sequence of heart electrical impulse activation
- abnormality in the rate, site of origin or conduction pathway of impulse

Arrhythmias





Physiological contraction



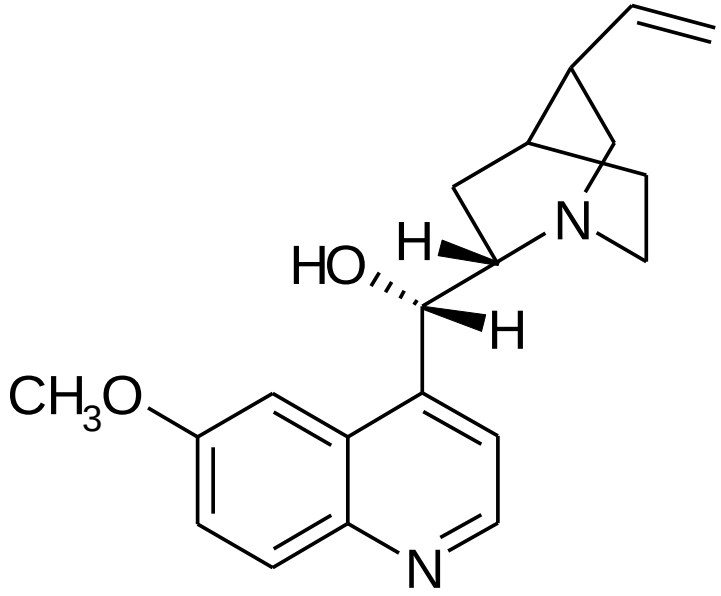
Arrhythmia therapy

- Invazive: intracardial cardiostimulators, defibrilators
- Medication: antiarrhythmics

Antiarrhythmics: classification

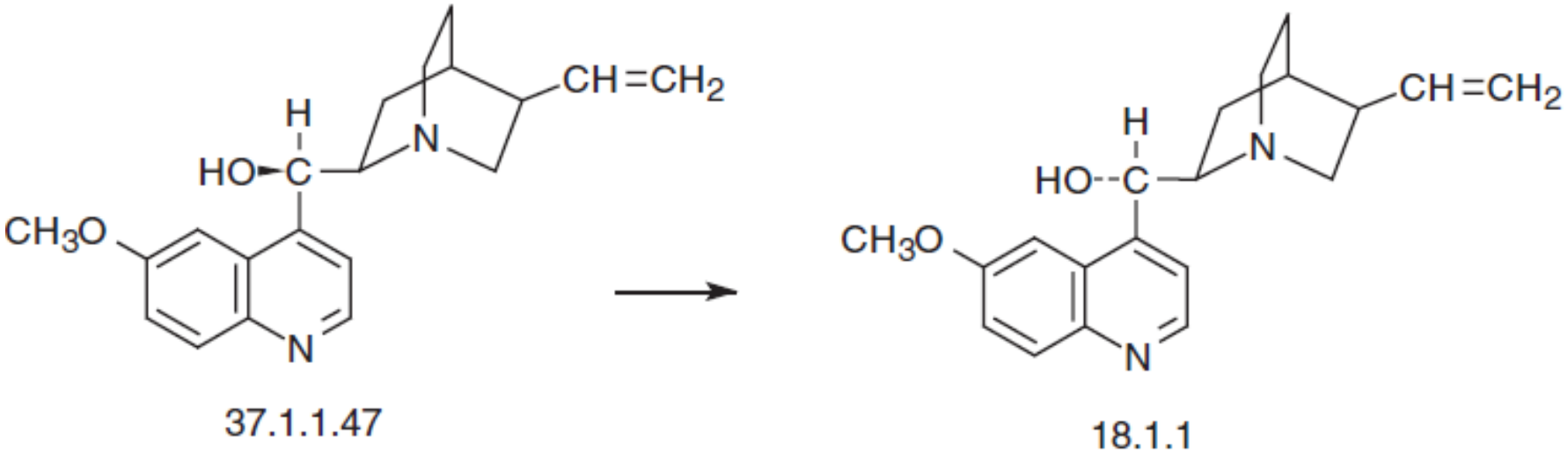
Class	Agent	Primary Pharmacologic Effect
IA	Quinidine Procainamide Disopyramide	Decrease maximal rate of depolarization; increases duration of action potential
IB	Lidocaine Phenytoin Tocainide Mexiletine	Decrease maximal rate of depolarization; decrease duration of action potential
IC	Flecainide Encainide Propafenone Moricizine	Decrease maximal rate of depolarization; no change in duration of action potential
II	Propranolol	Inhibition of sympathetic activity
III	Sotalol Ibutilide Bretylium Amiodarone	Prolongation of duration of action potential
IV	Verapamil Diltiazem Bepridil	Inhibition of inward slow calcium current

Class I A.



Quinidine

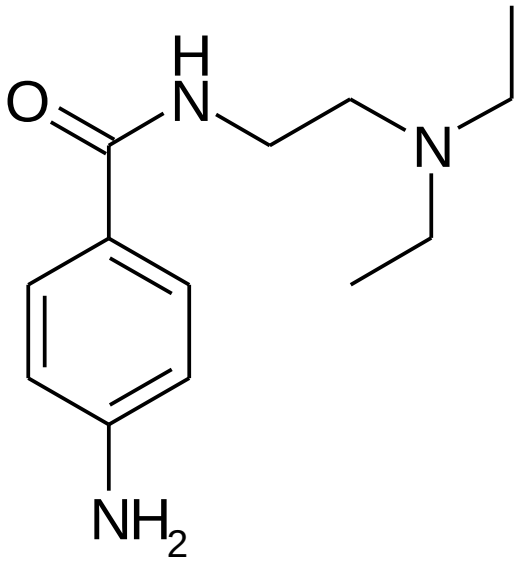
Quinidine synthesis



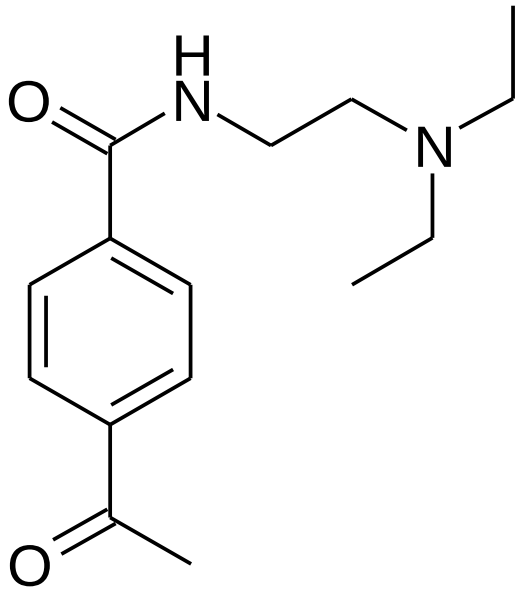
37.1.1.47

18.1.1

Class I A.

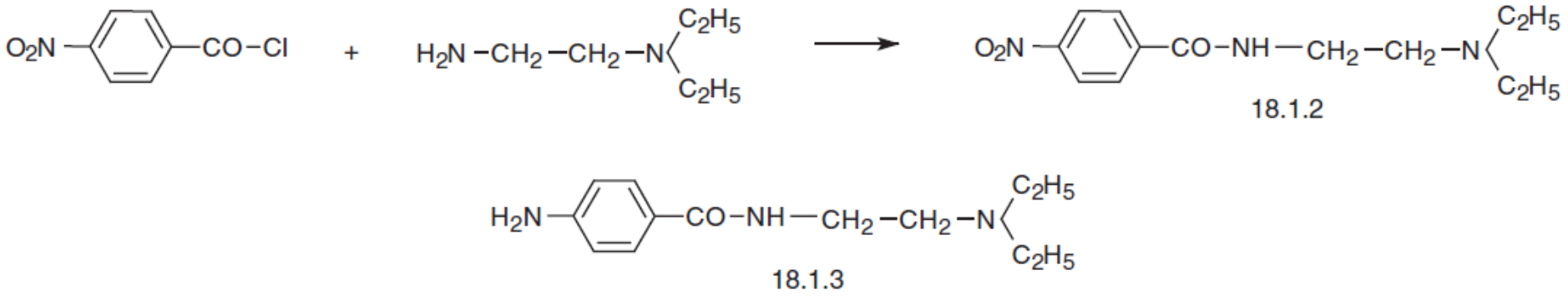


Procainamide

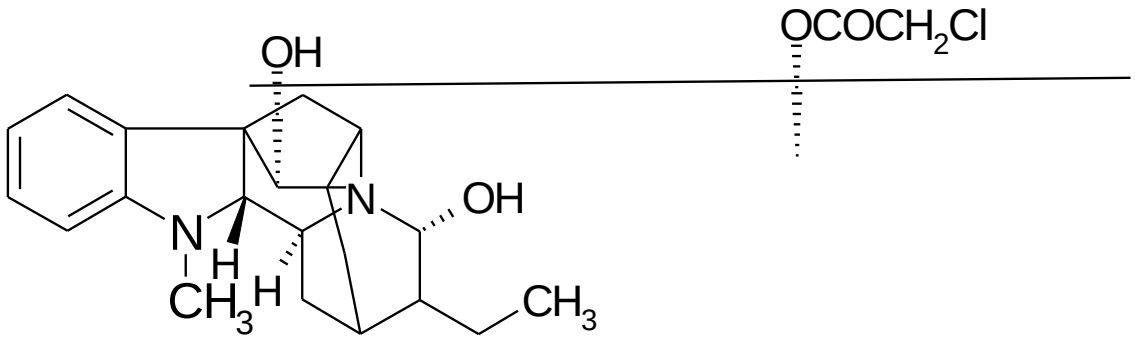


Acekainid

Procainamide synthesis

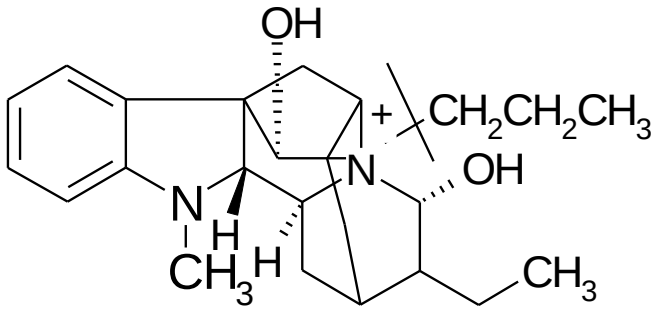


Class I A.

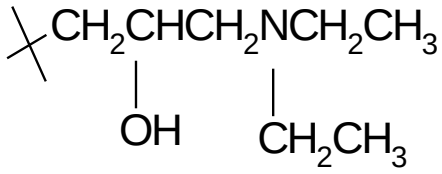


ajmalin

lorajmin

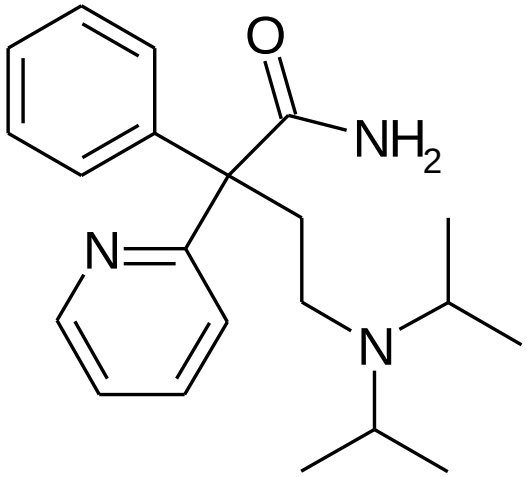


prajmalium

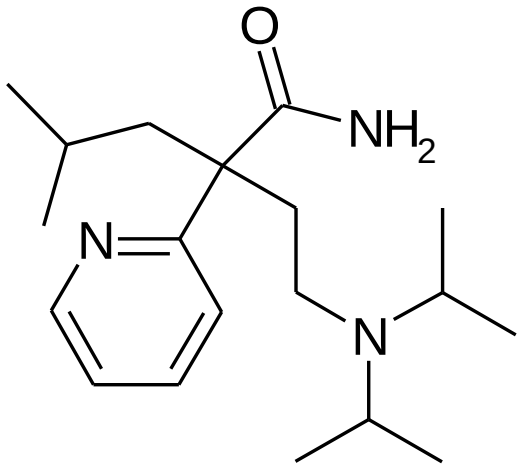


detajmium

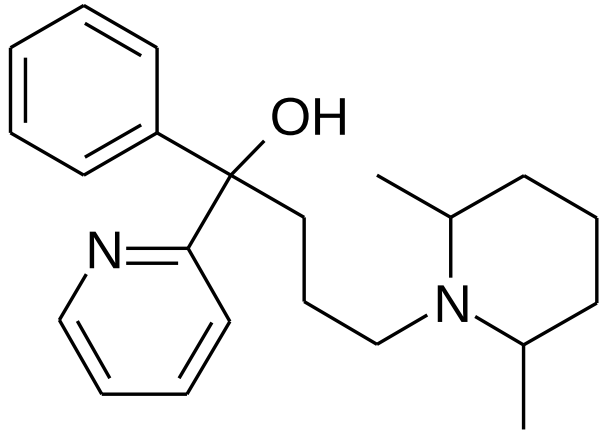
Class I A.



Disopyramide

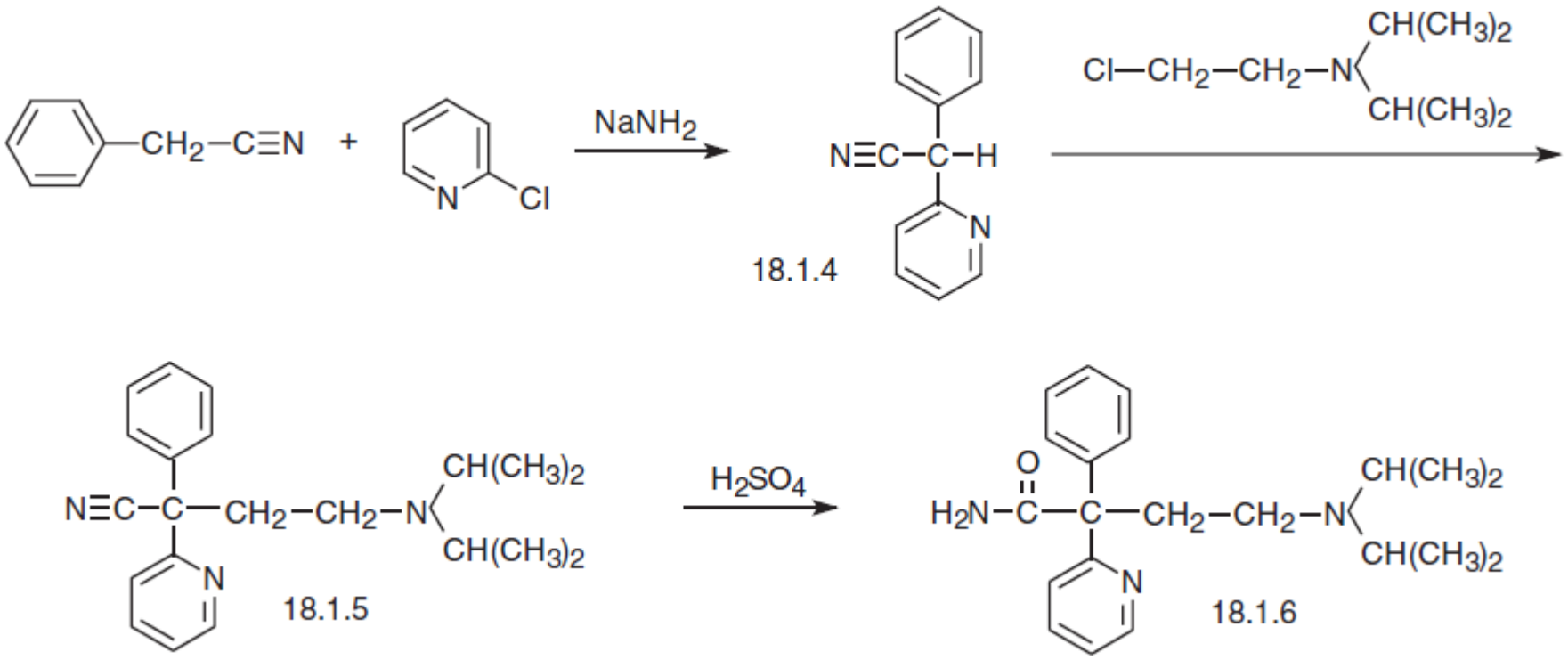


Pentisomide

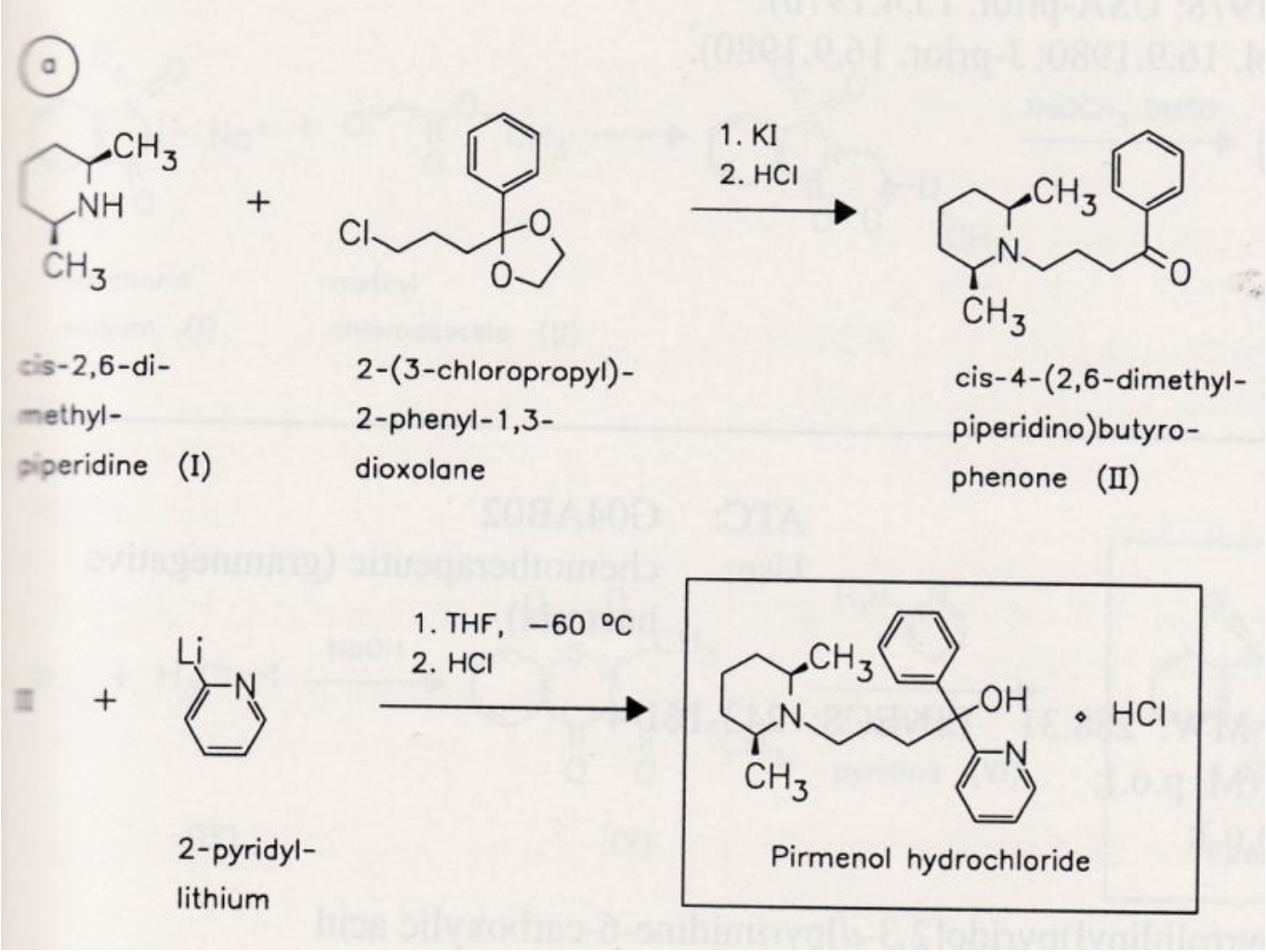


Pirmenol

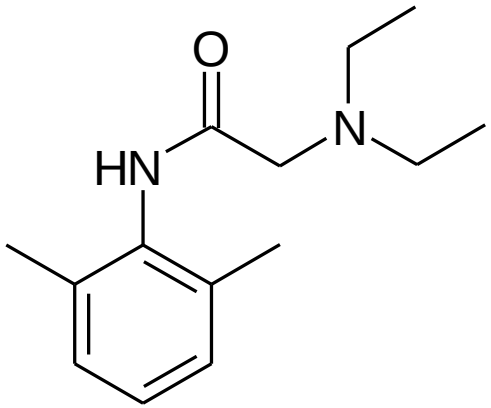
Disopyramide synthesis



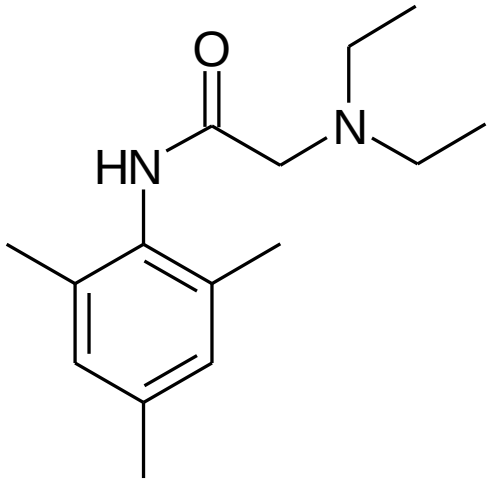
Pirmenole synthesis



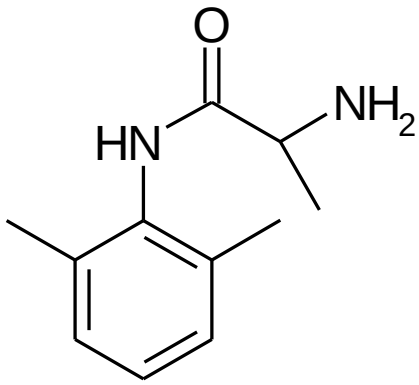
Class I B.



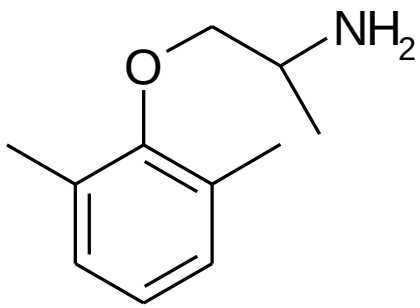
Lidocain



Trimecain

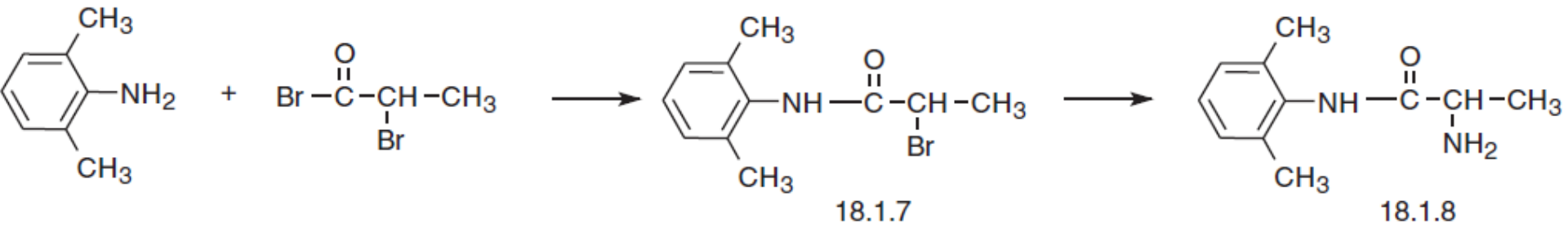


Tocainide

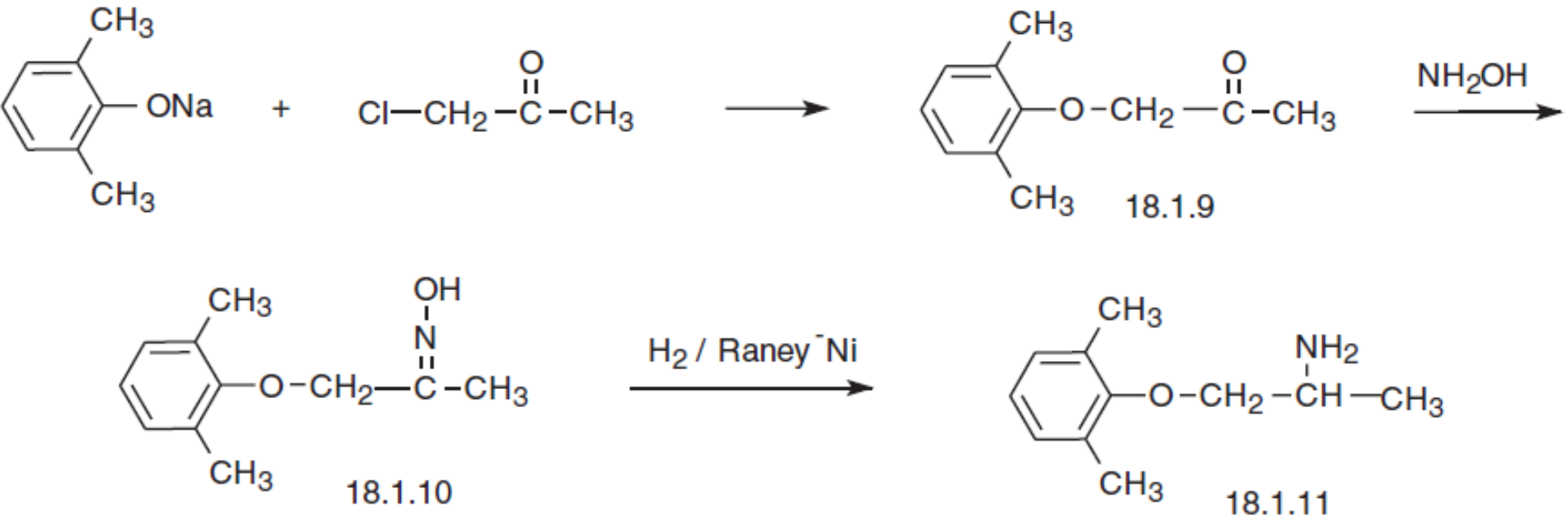


Mexilethine

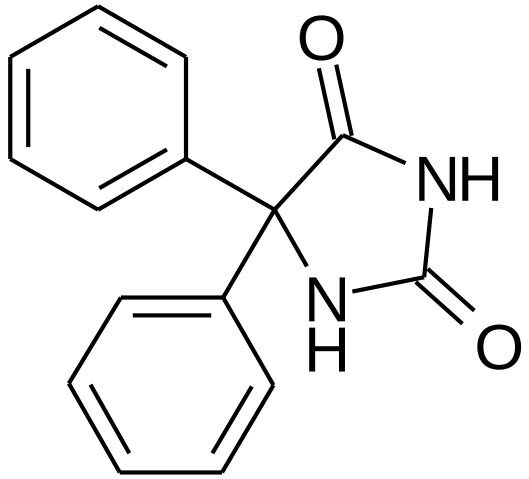
Tocainide synthesis



Mexilethine synthesis

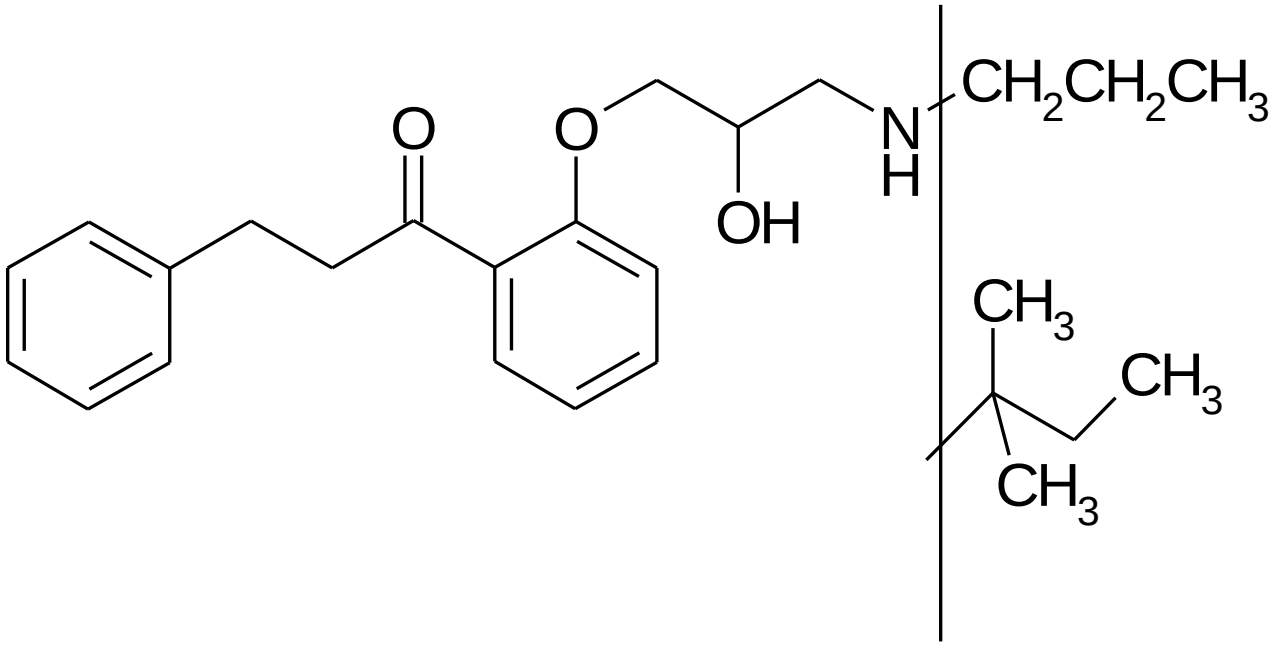


Class I B.



Phenytoin

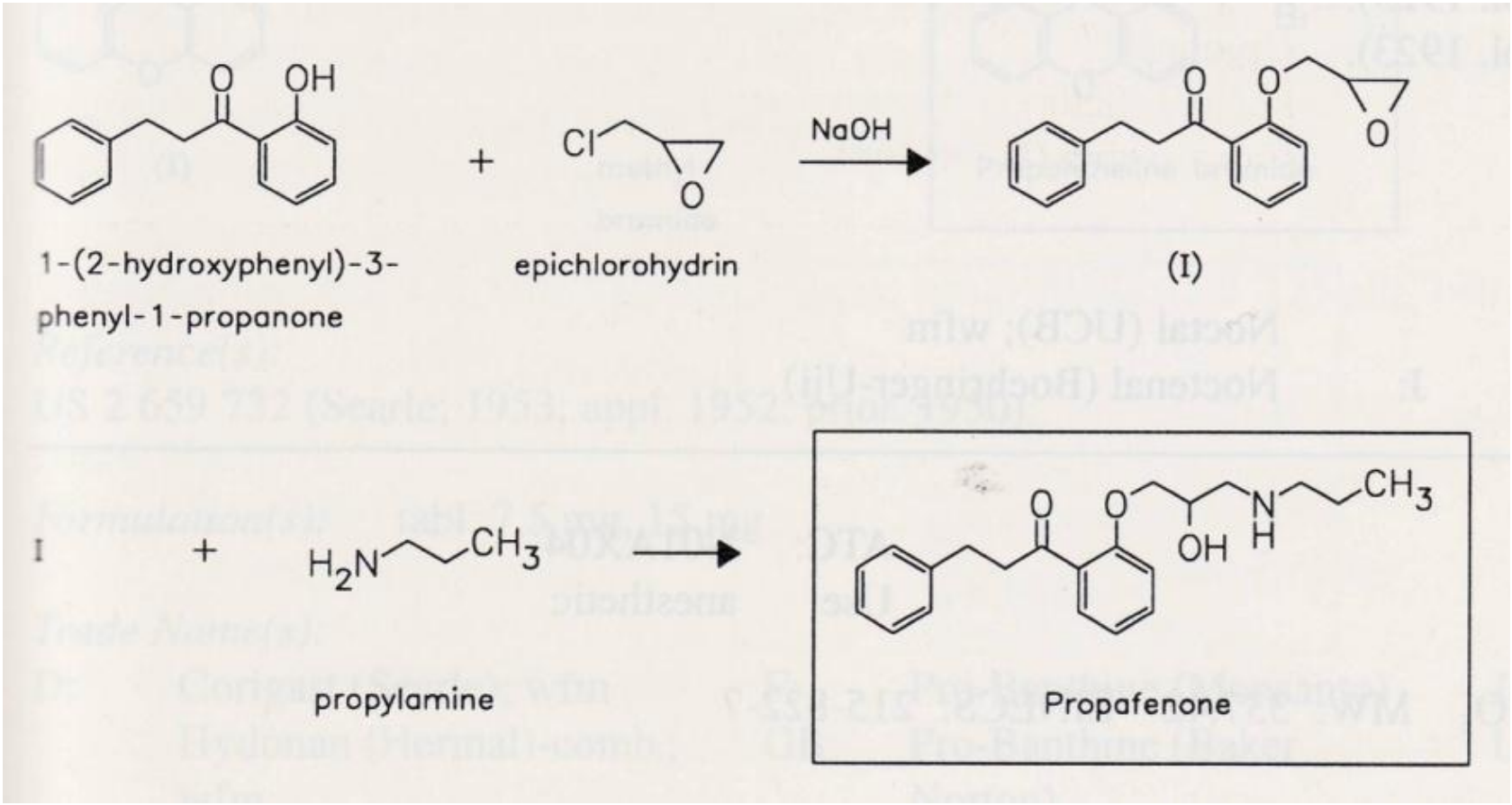
Class I C.



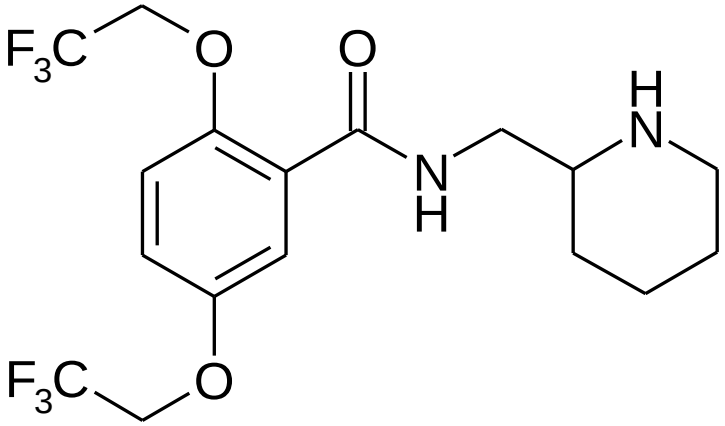
propaphenon

dipraphenon

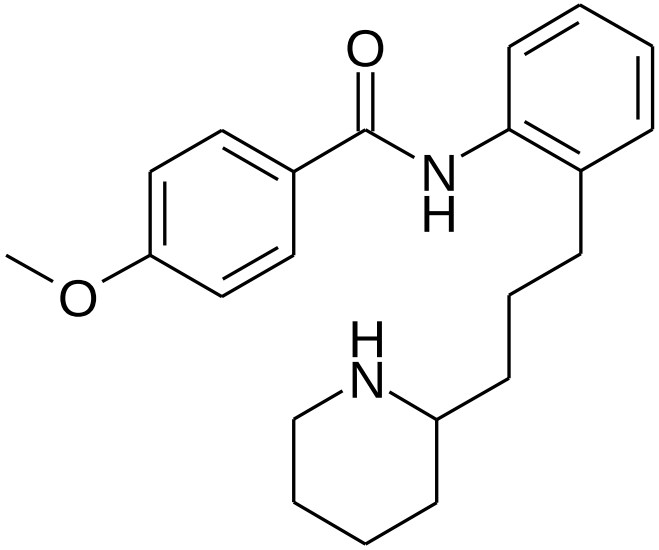
Propaphenone synthesis



Class I C.

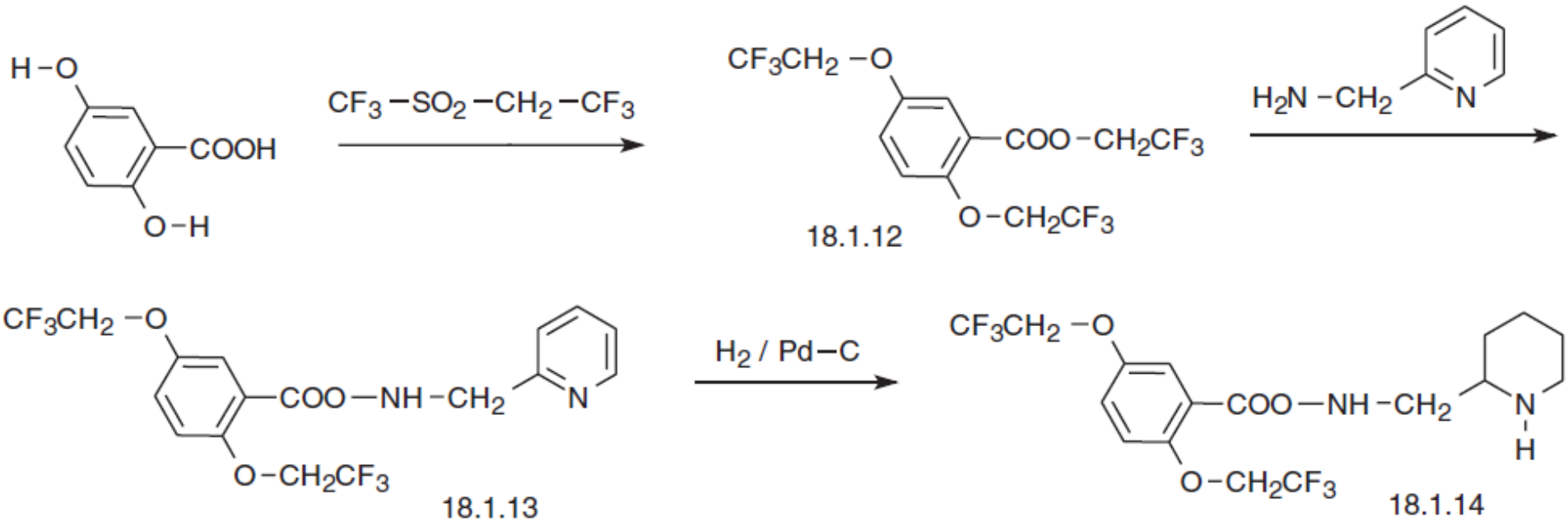


Flecainide

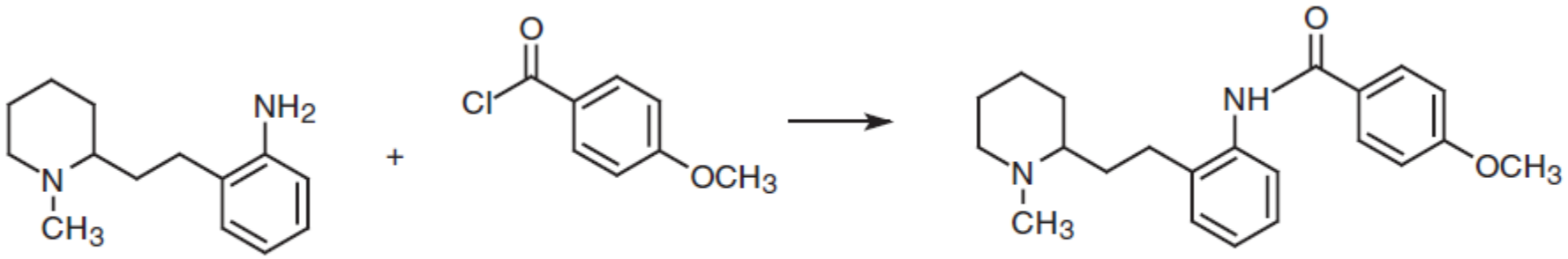


Encainide

Flecainide synthesis

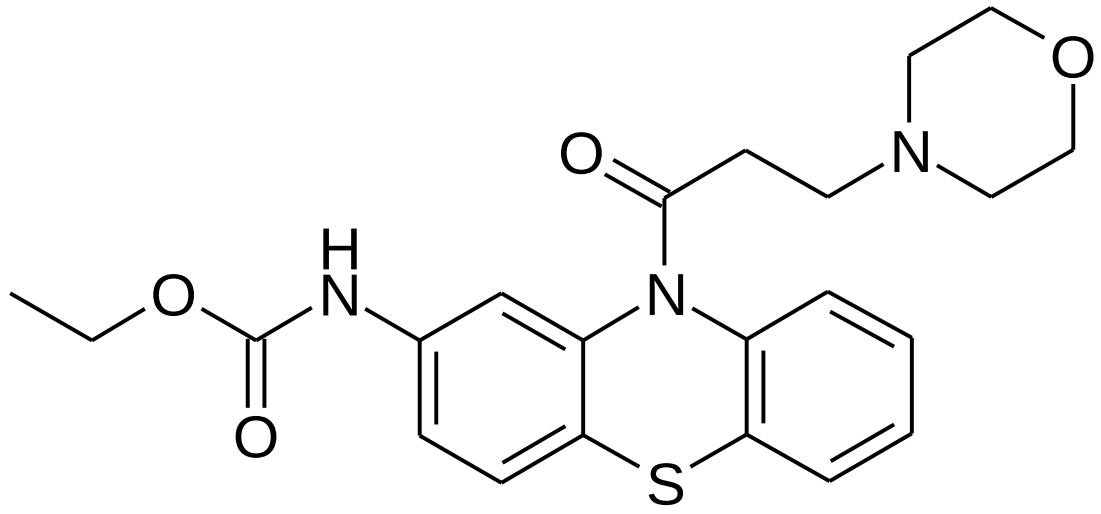


Encainide synthesis



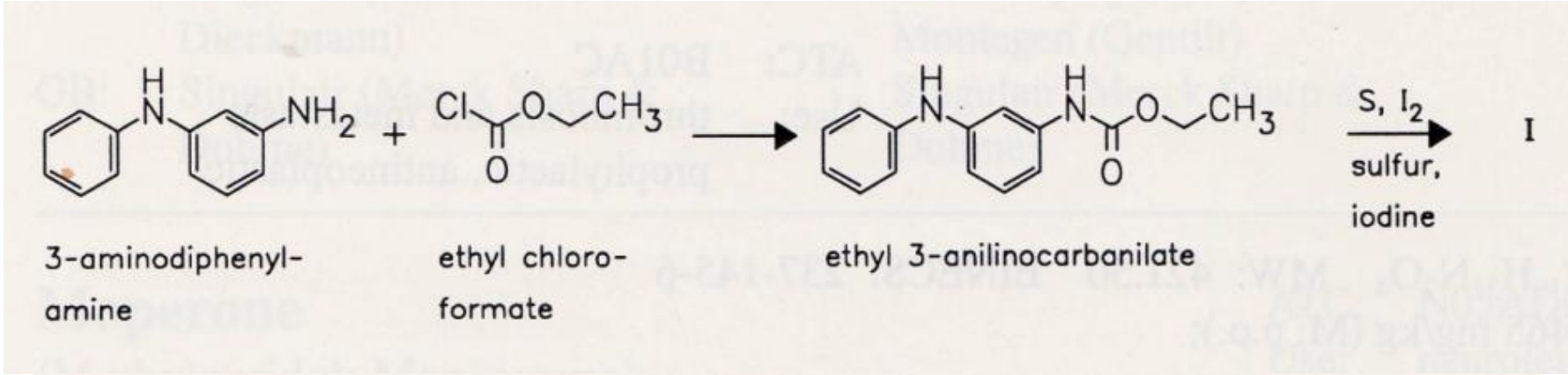
18.1.15

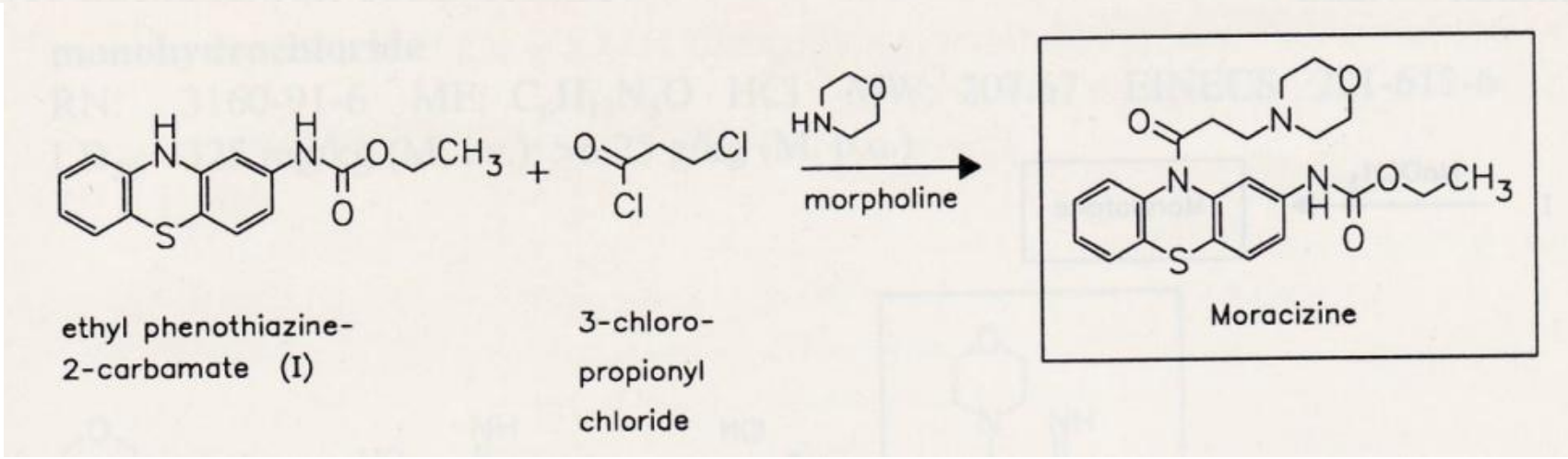
Class I C.



Morizicine

Moricizine synthesis

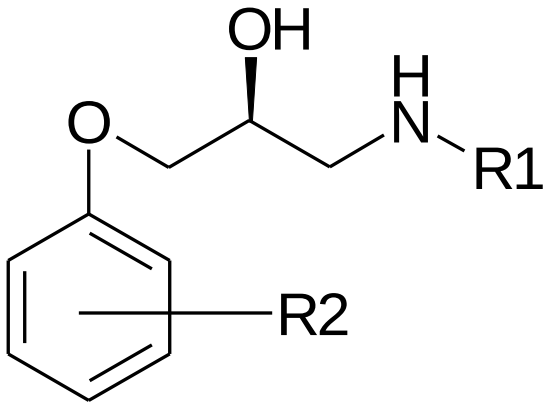




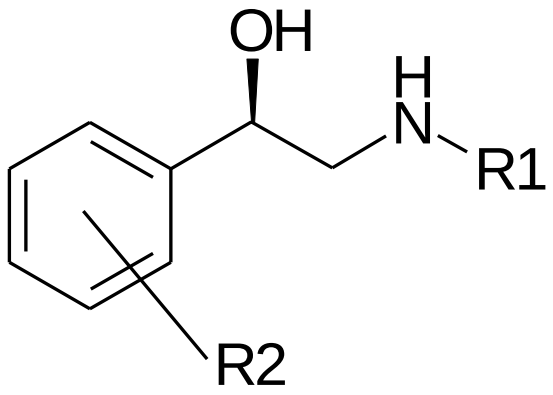
Class II.

- 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

SAR: (-propoxy-) spacer -O- can be replaced by isosteric -COO-; -NHCOO- or =C=N- group

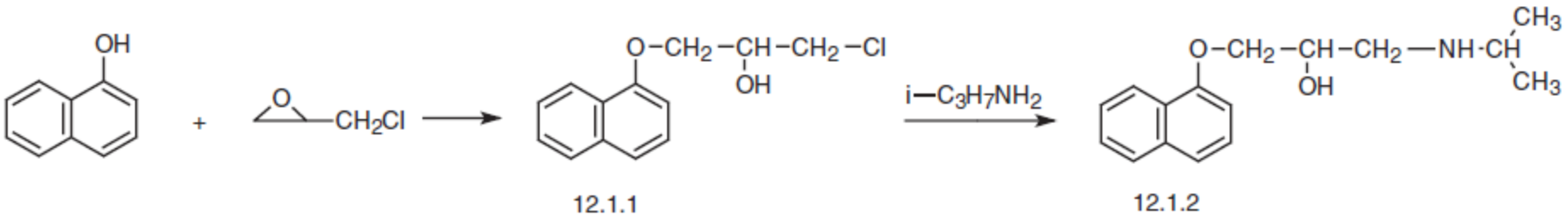
R1: isopropyl-, isobutyl- or arylalkyl-

R2: various substituents

o-substitution or another ring = non-selective

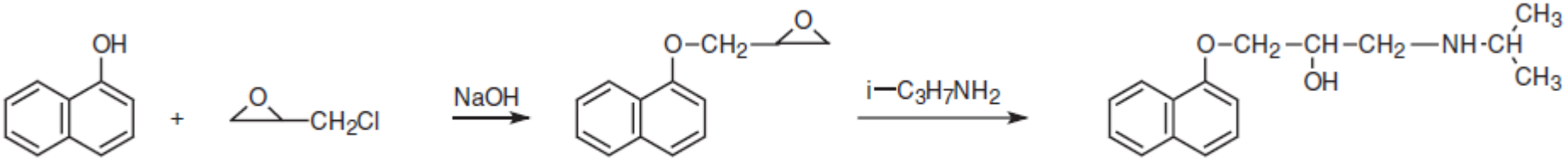
p-substitution = cardioselectivity

example of synthesis



12.1.1

12.1.2

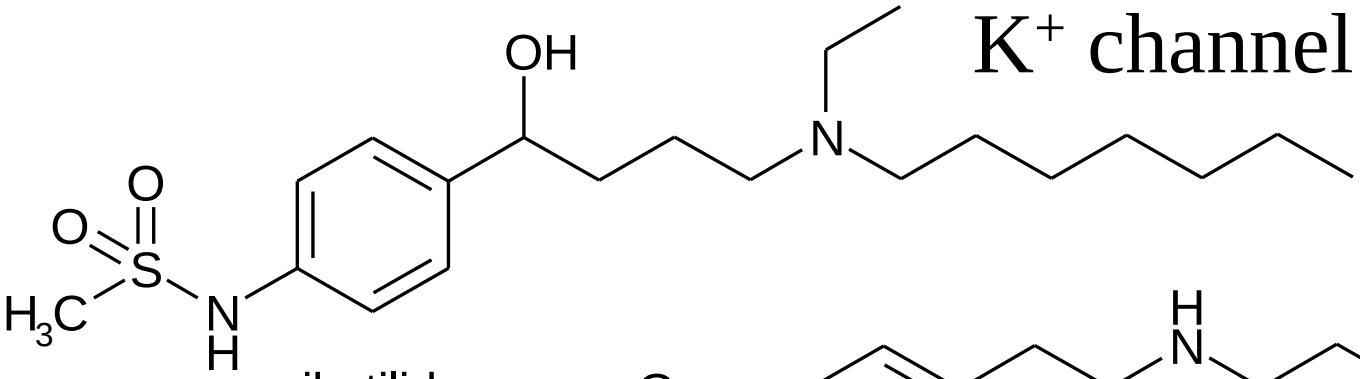


12.1.3

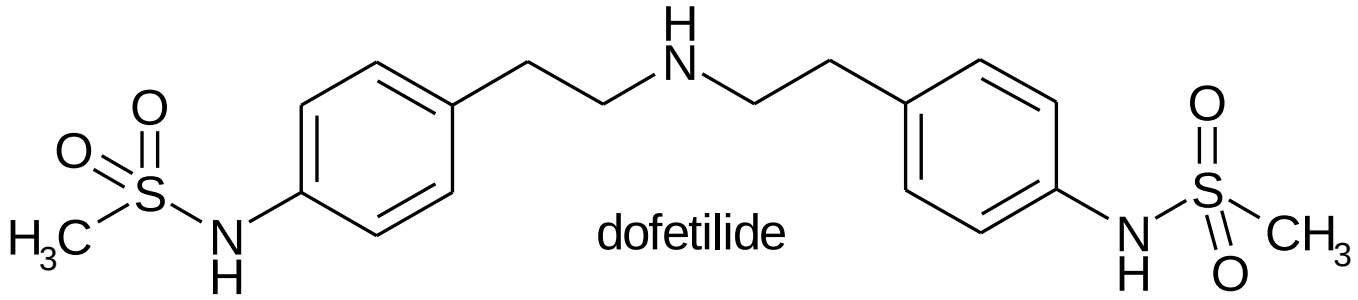
12.1.2

Class III.

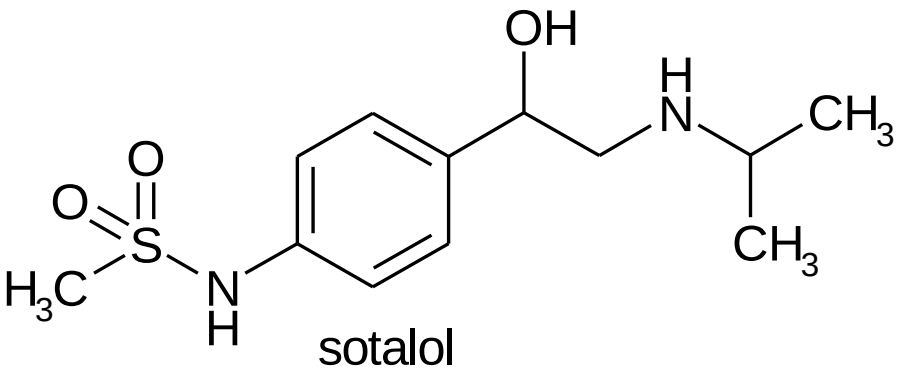
K^+ channel inhibitors



ibutilide

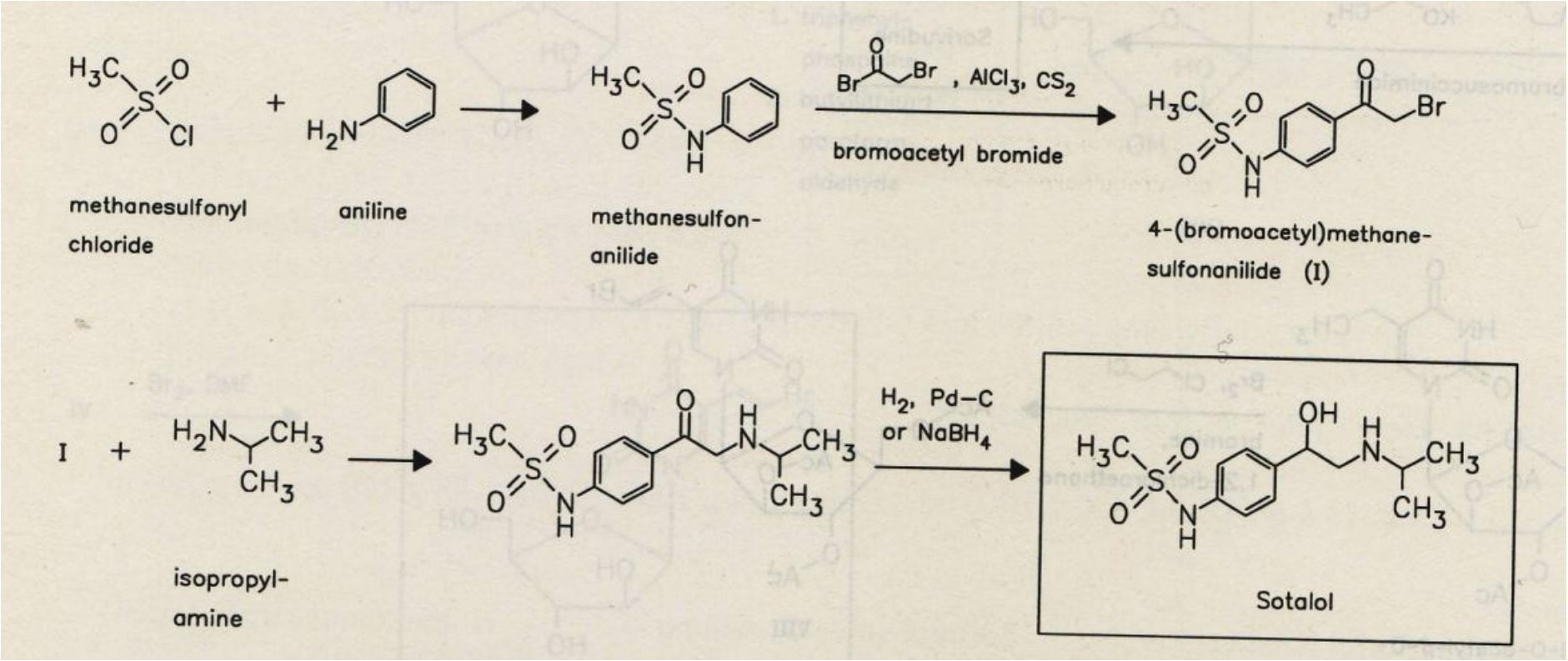


dofetilide

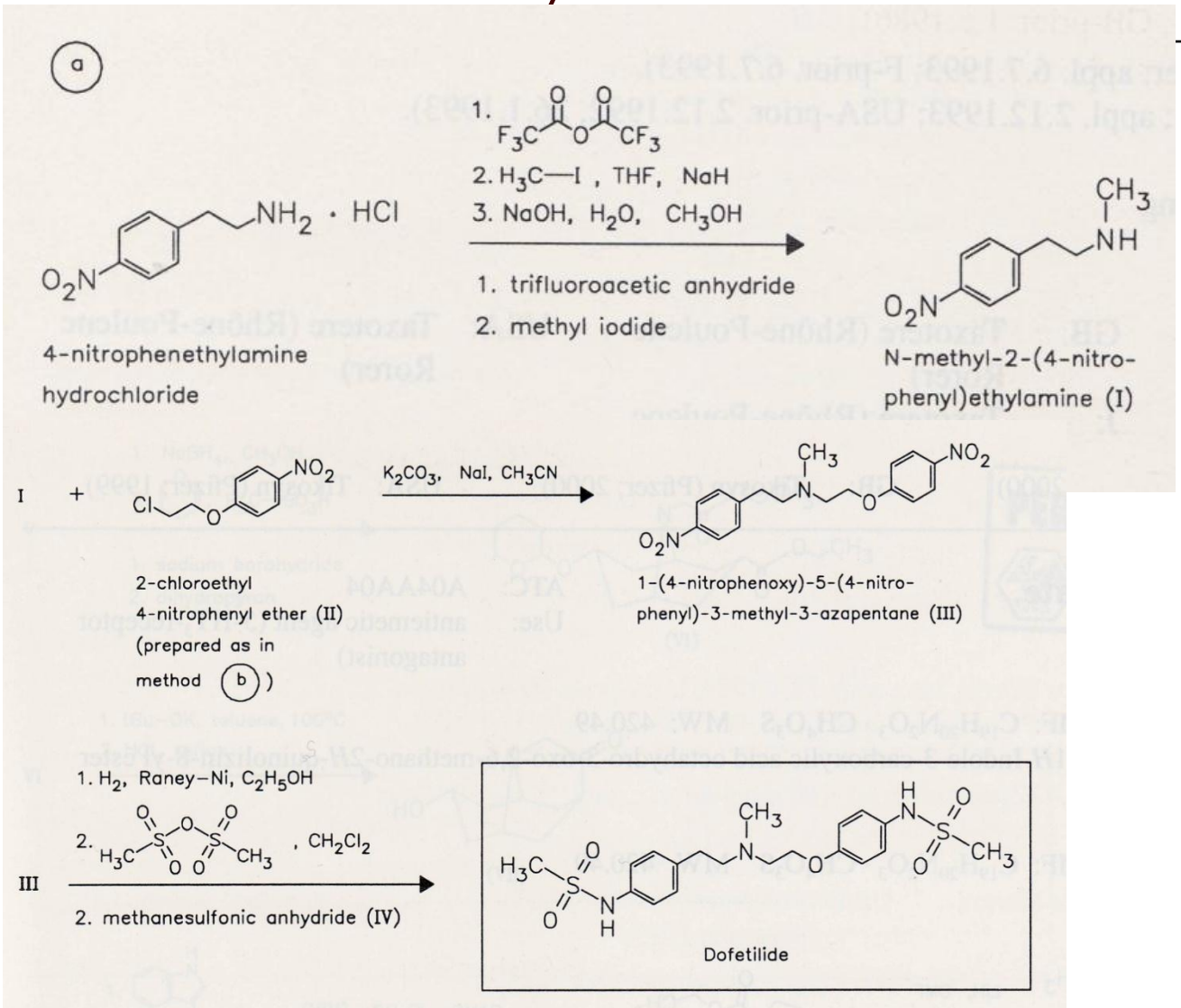


sotalol

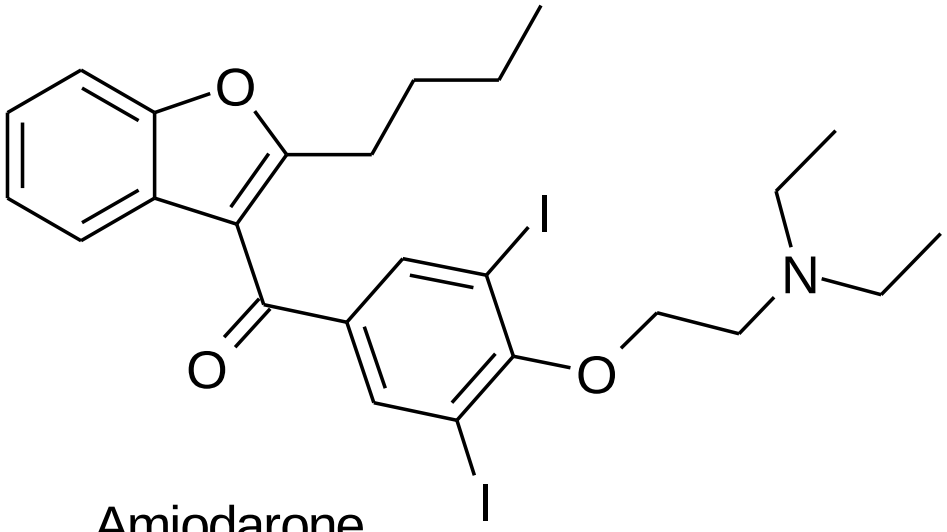
Sotalol synthesis



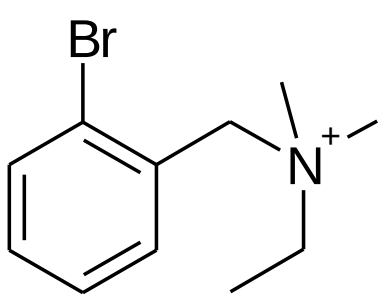
Dofetilide synthesis

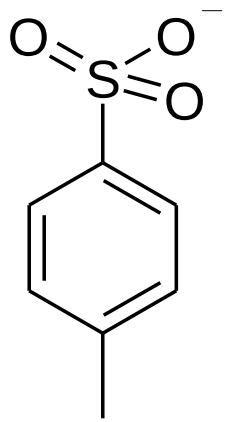


Class III.



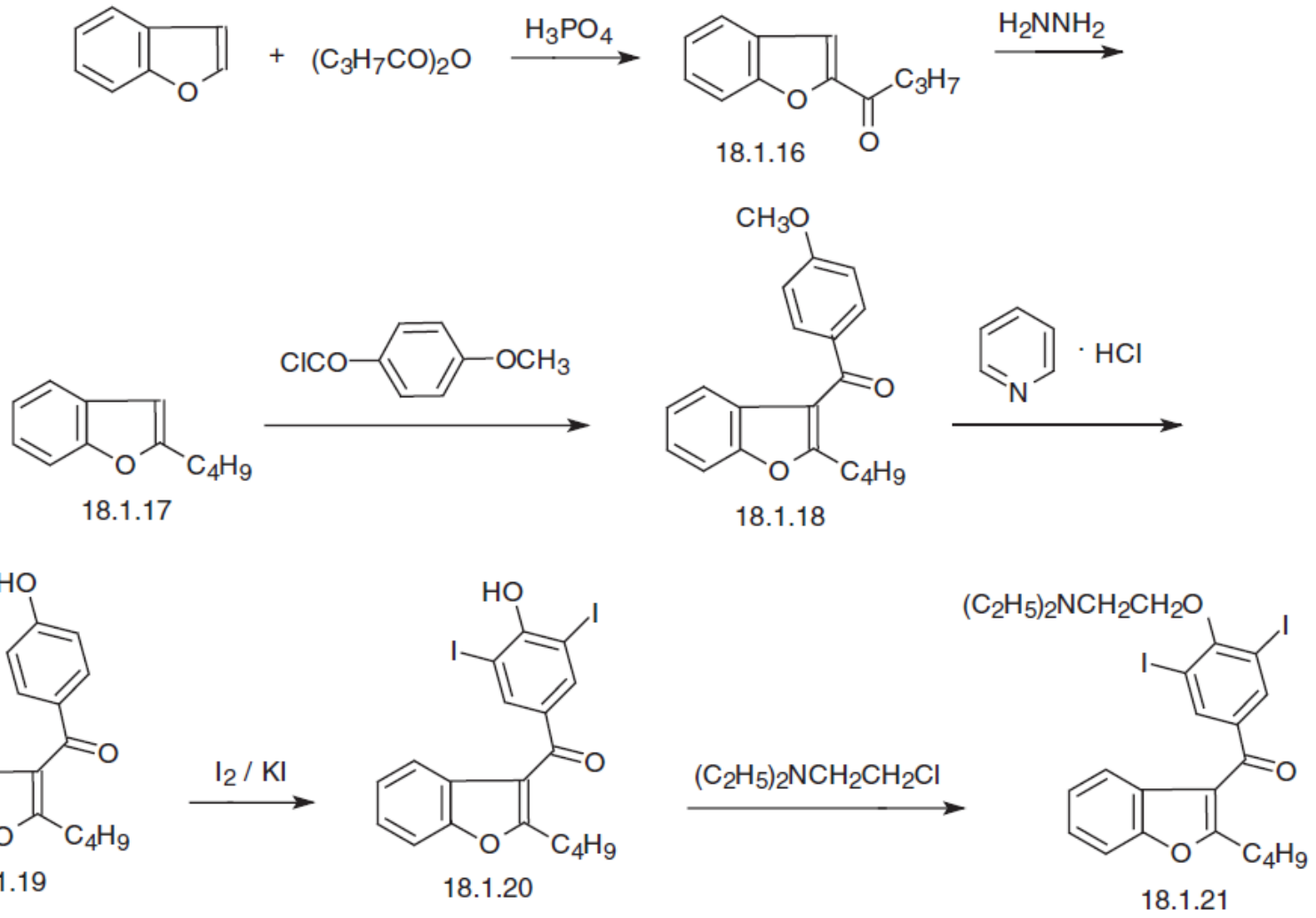
Amiodarone



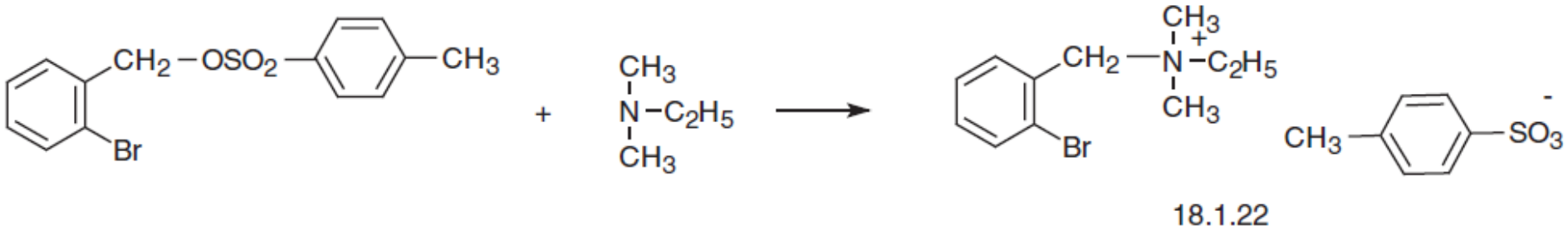


Bretylium tosylate

Amiodarone synthesis



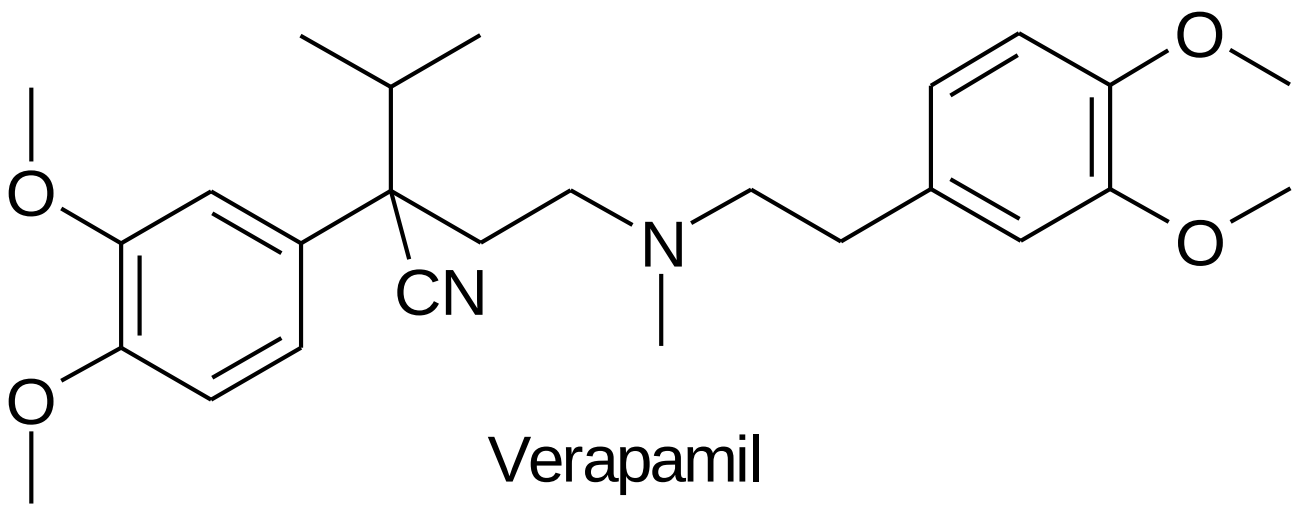
Bretylium tosylate synthesis



18.1.22

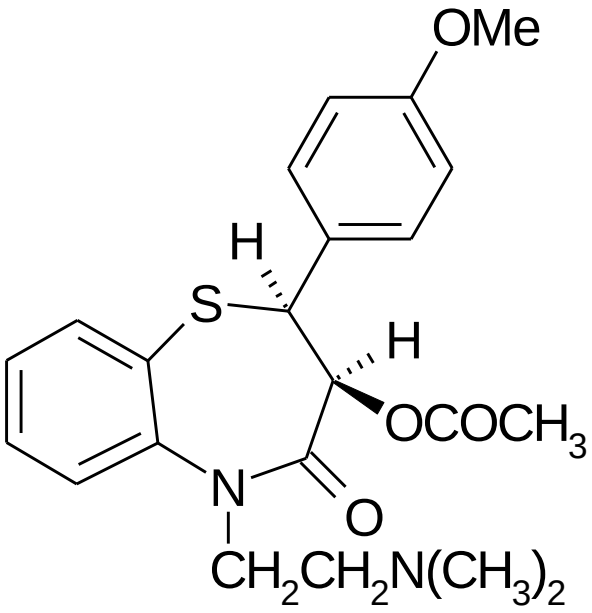
Class IV.

- Ca^{2+} channel blockers

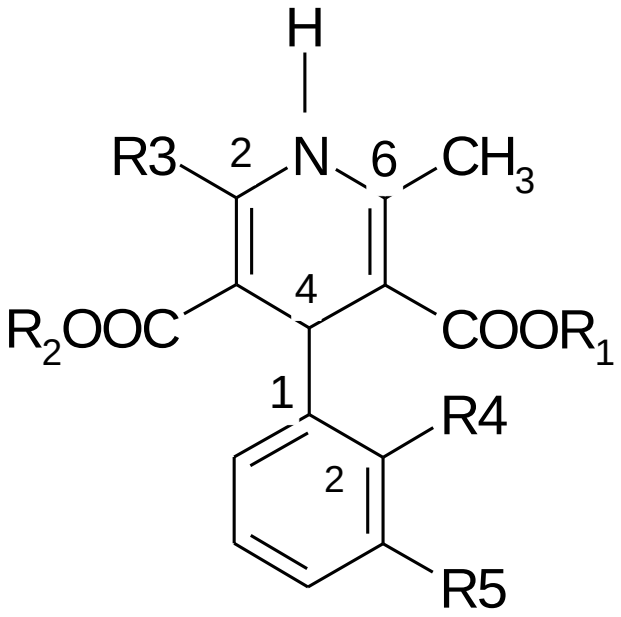


Verapamil

Class IV.



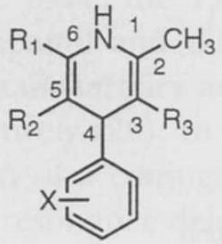
diltiazem



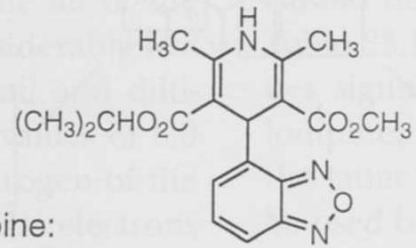
DIHYDROPYRIDINES

Class IV.

General structure:



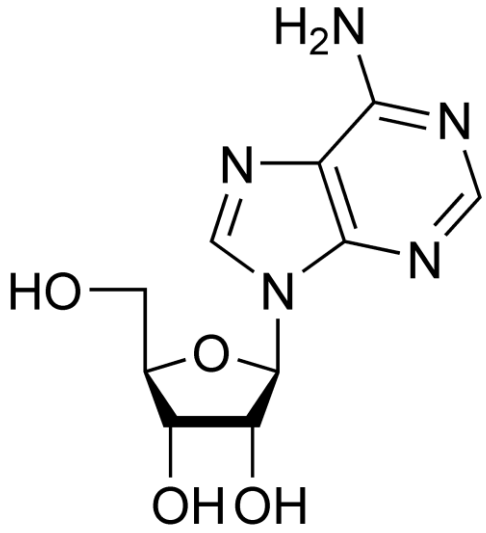
Isradipine:



Compounds	R_1	R_2	R_3	X
Amlodipine	$CH_2OCH_2CH_2NH_2$	$CO_2CH_2CH_3$	CO_2CH_3	2-Cl
Felodipine	CH_3	$CO_2CH_2CH_3$	CO_2CH_3	2,3-Cl_2
Nicardipine	CH_3	$CO_2CH_2CH_2$–NH–CH_2·C_6H_5	CO_2CH_3	3-NO_2
	CH_3	CH_3		
Nifedipine	CH_3	CO_2CH_3	CO_2CH_3	2-NO_2
Nimodipine	CH_3	$CO_2CH_2CH_2OCH_3$	$CO_2CH(CH_3)_2$	3-NO_2
Nisoldipine	CH_3	$CO_2CH_2CH(CH_3)_2$	CO_2CH_3	2-NO_2

Drugs within classification

- digoxin – *see cardiotonics*
- adenosine



- both prolongs duration of action potential